PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07H 15/00 | A2

(11) International Publication Number: **WO 98/08854**

(43) International Publication Date: 5 March 1998 (05.03.98)

(21) International Application Number: PCT/EP97/04649

(22) International Filing Date: 26 August 1997 (26.08.97)

(30) Priority Data:

60/024,556	26 August 1996 (26.08.96)	US
08/744,744	28 October 1996 (28.10.96)	US
08/764,315	12 December 1996 (12.12.96)	US
Not furnished	18 July 1997 (18.07.97)	US

(71) Applicants *(for all designated States except US)*: NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). THE SCRIPPS RESEARCH INSTITUTE [US/US]; 10666 North Torrey Pines Road, La Jolla, CA 91037 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: WONG, Chi-Huey [US/US]; 6399 Calle del Alcazar, P.O. Box 8154, Rancho Santa Fee, CA 92067 (US). LIN, Chun-Cheng [Stateless/US]; 5405 Baltimore Drive #73, La Mesa, CA 91942 (US). WOLTERING, Thomas, J. [DE/DE]; Lortzingstrasse 17, D-59558 Lippstadt (DE). MARRON, Thomas, G. [DE/DE]; Riedlistrasse 13, D-79576 Weil am Rhein (DE). MORIS-VARAS, Francisco [ES/US]; 3737 Novel Drive #2103, San Diego, CA 92122 (US). JABLONOWSKI, Jill [US/US]; 9898 Erma Road #61, San Diego, CA 92121 (US). WEITZ-SCHMIDT, Gabriele [DE/DE]; Steinbrecherstrasse 4, D-79189 Bad Krozingen (DE).

(74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: ORGANIC COMPOUNDS

(57) Abstract

Sialyl Lewis X mimetics which mimic the inhibition of selectin-mediated cellular adhesion by sialyl Lewis X having a core of formula (I).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Organic compounds

The present invention relates to compounds that inhibit cellular adhesion. More particularly, the present invention relates to sialyl Lewis X mimetics which mimic the inhibition of selectin-mediated cellular adhesion by sialyl Lewis X.

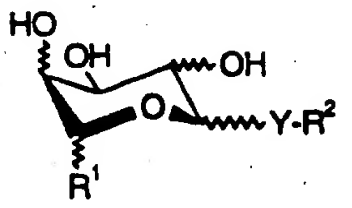
The complex process of inflammation, which takes place in several stages, is the body's natural reaction to injuries in which, for example, there is also invasion by infectious agents. Under the influence of cytokines, the endothelium which lines the blood vessels expresses adhesion proteins on its surface. The P and E selectins bring about, by a protein-carbohydrate interaction with glycolipids and glycoproteins on the leukocyte membrane, the so-called "rolling" of leukocytes. The latter are slowed down by this process, and there is activation of certain proteins (integrins) on their surface which ensure firm adhesion of the leukocytes to the endothelium. This is followed by migration of the leukocytes into the damaged tissue.

There are many situations in which the recruitment of leukocytes by adhesion to the endothelial cells is abnormal and in excess resulting in tissue damage instead of repair. This is the case in disorders such as cardiogenic shock, myocardial infarct, thrombosis, rheumatism, psoriasis, arthritis, dermatitis, acute respiratory distress syndrome, metastatic cancer and transplantation.

One of the smallest natural carbohydrate epitopes as ligand for E selectin is sialyl-Lewis X [neuraminic acid-α(2→3)-D-galactose-β(1→4)-L-(fucose-α(1→3))-N-acetyl-D-glucosamine (sLe^x)]. Although it has been considered to be potentially useful as an antiinflammatory agent it can only be used as an injectable form as it is orally inactive and has a short half-life in blood. Thus, there is a need for compounds which prevent the interaction between P and E selectins and their receptors on the leukocyte membrane and which prevent the initial cellular adhesion process.

What are needed are SLe^x mimetics which are easy to synthesize, more stable and more active than SLe^x, and preferably orally active.

The present invention relates to compounds of formula I



(I)

wherein

(a) R^1 is CH_3;

Y is C_1-C_4alkylene which is unsubstituted or substituted by one or two substituents selected from OR^3 and $C(O)NH[CH_2]_mC(O)NHC_{10}$-$C_{16}$alkyl;

R^2 is $-NR^6R^7$;

R^3 is aralkyl with C_1-C_8alkyl and C_6-C_{10}aryl or $CH_2C(O)NHC_1$-C_{20}alkyl which is unsubstituted or substituted by one or two $OC(O)C_{10}$-C_{16}alkyl;

R^6 is $C(O)CHR^8NHC(O)(CH_2)_qC(O)OH$;

R^7 is H or $(CH_2)_mC(O)NHC_{10}$-C_{16}alkyl;

R^8 is C_1-C_6alkyl unsubstituted or substituted with one or two OH;

m is a number from 1 to 6; and

q is 2 or 3; or

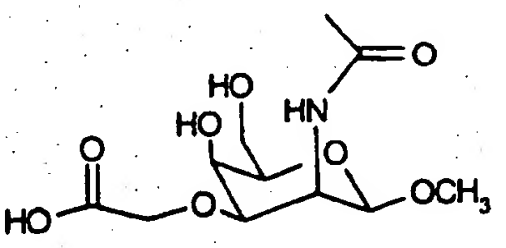
(b) R^1 is OH;

Y is $-CH_2-$;

R^2 is $-NR^6H$; and

R^6 is $C(O)$-C_1-C_{30}alkyl which is substituted by C(O)OH; or

(c) R^1 is a group of formula Ia



(Ia)

Y is $-CH_2-$; and

R^2 is OH; or

(d) R^1 is Y'-$R^{2'}$;

Y is $-CH_2-$;

R^2 is OH, $-O$-C_4-C_{30}alkyl or NHR^6;

Y' is $-CH_2-$ or $-O-CH_2-$;

$R^{2'}$ is -CHOHCHOHC(O)$(CH_2)_nR^5$; -CHOHCHOHC(O)$[CH_2]_nC(O)OH$; -CHOHCHOHC(O)CH_2CH[benzyl]C(O)OH; -CHOHCHOHC(O)$NH(CHR^4)_nC(O)OH$; -C(O)$NHCH_2C(O)OH$; C(O)$NHCHR^4C(O)OH$; -C(O)NHC_2-C_4alkyl which is substituted by two C(O)OH or -C(O)NHphenyl which is substituted by one C(O)OH;

R^4 is H, C_1-C_6alkyl which is substituted by C(O)OH; CH_2hydroxyphenyl or benzyl;

R^5 is OPO_3H_2 or PO_3H_2;

R^6 is C_4-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl, aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl, O-C_4-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl, O-C_4-C_{30}alkenyl with 1 to 3 double bonds, O-C_6-C_{10}aryl, C(O)-C_1-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl or C(O)OH, C(O)-C_4-C_{30}alkenyl with 1 to 3 double bonds, $C(O)(CHR^8)_pNHC(O)(CH_2)_qC(O)OH$, $C(O)(CH_2)_mNHC_1$-C_6alkyl, or $C(O)(CH_2)_rCON(CH_2CONH(CH_2)CH_3)HCONH(CH_2)_sCH_3$;

R^8 is H or C_1-C_6alkyl unsubstituted or substituted with one or two OH;

m is a number from 1 to 6;

n is 1 or 2; and

the sum of p and q as well as of r and s has a value of from 2 to 22;

including their physiologically tolerated salts.

The compounds of formula I may comprise one or more asymmetric carbon atoms. It will be understood that the present invention includes all individual isomeric forms, enantiomers and diastereoisomers as well as mixtures, e.g. racemates, unless otherwise stated.

A preferred embodiment comprises compounds of group (a) wherein R^1 is CH_3; Y is C_1-C_4alkylene which is substituted by one or two OR^3; R^2 is $-NHR^6$; R^3 is aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl or $CH_2C(O)NHC_1$-C_{20}alkyl which is unsubstituted or substituted by one or two $OC(O)C_{10}$-C_{16}alkyl; R^6 is $C(O)(CHR^8)_pNHC(O)(CH_2)_qC(O)OH$; R^8 is C_1-C_6alkyl unsubstituted or substituted with one or two OH; p is 1; and q is 2 or 3. Most preferred compounds are **1**, **2**, **3b**, **4**, **5b** and **6b** as exemplified in Examples B.

Another preferred embodiment comprises compounds of group (a) wherein R^1 is CH_3; Y is C_1-C_4alkylene which is substituted by one or two OR^3; R^2 is $-NR^6R^7$; R^3 is aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl or $CH_2C(O)NHC_1$-C_{20}alkyl which is unsubstituted or substituted by one or two $OC(O)C_{10}$-C_{16}alkyl; R^6 is $C(O)(CHR^8)_pNHC(O)(CH_2)_qC(O)OH$; R^7 is $(CH_2)_mC(O)NHC_{10}$-C_{16}alkyl; R^8 is C_1-C_6alkyl unsubstituted or substituted with one or two OH;

p is 1; and q is 2 or 3. Most preferred compounds are **7**, **8** and **79(3)** as exemplified in Examples B.

Within group (b) the most preferred compounds are **27(15)** and **29(15)** as exemplified in Examples B.

Within group (c) the most preferred compounds are **19(15)**, **24(15)** and **1(3)** as exemplified in Examples B.

Another preferred embodiment comprises compounds of group (d) wherein R^1 is Y'-$R^{2'}$; Y is -CH_2-; Y' is -CH_2- or -O-CH_2-; R^2 is OH; $R^{2'}$ is CHOHCHOHC(O)$(CH_2)_nR^5$; R^5 is OPO_3H_2 or PO_3H_2; and n is 1 or 2. Most preferred compounds are **6(14)**, 4(3), **4a(3)**, **7(14)** and **13(14)** as exemplified in Examples B.

Another preferred embodiment comprises compounds of group (d) wherein R^1 is Y'-$R^{2'}$; Y is -CH_2-; R^2 is OH; Y' is -CH_2-; $R^{2'}$ is -CHOHCHOHC(O)$(CH_2)_2$C(O)OH; -CHOHCHOHC(O)CH_2CH[benzyl]C(O)OH; -CHOHCHOHC(O)NHCHR^4C(O)OH; -C(O)NHCH_2C(O)OH or C(O)NHCHR^4C(O)OH; and R^4 is H, C_1-C_6alkyl which is substituted by C(O)OH; CH_2hydroxyphenyl or benzyl. Most preferred compounds are **5(15)**, **6(15)**, **102(3)**, **103(3)**, **104(3)**, **105(3)** and **106(3)** as exemplified in Examples B.

Another preferred embodiment comprises compounds of group (d) wherein R^1 is Y'-$R^{2'}$; Y is -CH_2-; Y' is -CH_2-; R^2 is -O-C_4-C_{30}alkyl and $R^{2'}$ is -C(O)NHC_2-C_4alkyl which is unsubstituted or substituted by two C(O)OH; or -C(O)NHphenyl which is substituted by one C(O)OH. Most preferred compounds are **3(3)** and **3a(3)** as exemplified in Examples B.

Another preferred embodiment comprises compounds of group (d) wherein R^1 is Y'-$R^{2'}$; Y is -CH_2-; Y' is -CH_2- or -O-CH_2-; R^2 is -NHR^6; $R^{2'}$ is - CHOHCHOHC(O)CH_2R^5 or C(O)NHCHR^4C(O)OH; R^5 is OPO_3H_2 or PO_3H_2; R^6 is C_4-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl, aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl, O-C_4-C_{30}alkyl; C(O)-C_1-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl or C(O)OH; C(O)$(CH_2)_p$NHC(O)$(CH_2)_q$C(O)OH; C(O)$(CH_2)_m$NHC_1-C_6alkyl; or C(O)$(CH_2)_n$CON$(CH_2CONH(CH_2)CH_3)$HCONH$(CH_2)_sCH_3$; m is a number from 1 to 6; n is 1 or

2; and the sum of p and q as well as of r and s has a value of from 2 to 22. Most preferred compounds are **39(3)**-**58c(3)**, **69(3)** and **72(3)** as exemplified in Examples B.

The present invention also comprises a process for the preparation of the compounds of the formula I wherein the corresponding radicals -Y-R^2 and -Y'-$R^{2'}$ are coupled, optionally via more than one step, to the corresponding sugar moiety. The procedures are generally known to the skilled person or can be deduced from the Examples, describing further non-limiting details of the preparation. Of particular interest is the coupling step within the synthesis of C-glycosides of group (d), eg. **6(14)** and **4(3)** which may be performed in the presence of a DHAP dependent aldolase. In a preferred mode, the DHAP substrate is a compound selected from the group consisting of e.g. dihydroxyacetone phosphate and 3-keto-4-hydroxy-butanyl-1-phosphonate. In an alternative preferred mode, the DHAP dependent aldolase is selected from the group consisting of FDPA, FucA, RhaA and TagA.

The compounds of formula I exhibit valuable pharmacological properties as indicated in tests and are therefore indicated for therapy. In particular the compounds of formula I inhibit the binding of E-selectin to HL-60 cells as disclosed in Example D.

The compounds are particularly indicated for preventing or treating conditions or diseases which are mediated by the binding of selectin in cellular adhesion, e.g. acute or chronic inflammatory or autoimmune diseases such as rheumatoid arthritis, asthma, allergy conditions, psoriasis, contact dermatitis, adult respiratory distress syndrome, inflammatory bowel disease and ophthalmic inflammatory diseases, infection diseases such as septic shock, traumatic shock, thrombosis and inappropriate platelet aggregation conditions, cardiovascular diseases such as heart attacks, reperfusion injury, multiple sclerosis and neoplastic diseases including metastasis conditions, strokes and acute or chronic rejection of organ or tissue transplants.

Acute and chronic rejection play a role in the transplantation of organs or tissues from a donor to a recipient of the same species (allograft) or different species (xenograft). Among such transplanted organs or tissues and given illustratively are heart, lung, combined heart-lung, trachea, liver, kidney, spleen, pancreatic (complete or partial, e.g. Langerhans islets), skin, bowel, or cornea or a combination of any of the foregoing.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired, In general, however, satisfactory results are achieved at dosage rates of from 0.1 to about 100 mg/kg/day, administered in 1, 2, 3, or 4 doses/day, or in sustained release form. Suitable daily dosages for oral administration to larger mammals, e.g., humans, are generally about 50 to 1500 mg, preferably in the order of from 200 to 800 mg. Unit dosage forms suitably comprise from about 25 mg to 0.750 g of a compound of the invention, together with a pharmaceutical acceptable diluent or carrier therefor.

The compounds of formula I may be administered by any conventional route of administration, e.g. enterally, preferably orally, e.g. in the form of tablets or capsules, or parenterally e.g. in form of injectable solutions or suspensions.

OPO_3H_2, PO_3H_2 and the carboxyl group may be in free acid form or in salt form. Pharmaceutically acceptable salts are to be understood as meaning, in particular, the alkali metal and alkaline earth metal salts, for example sodium, potassium, magnesium and calcium salts. Sodium and potassium ions and their salts are preferred.

In accordance with the foregoing the present invention further provides:
(a) a compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical;
(b) a method for preventing or treating conditions or diseases as indicated above in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
(c) a pharmaceutical composition comprising a pharmaceutically effective amount of the compound of formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier;
(d) a compound of formula I or a pharmaceutically acceptable salt thereof for use in the manufacturing of a medicament for use in the method as in (b) above.

The compound may be administered alone or in combination with one or more other anti-inflammatory or immunosuppressive agents, for example in combination with cyclosporin A and analogs thereof, FK-506 and analogs thereof, rapamycin and analogs thereof, myco-

phenolic acid, mycophenolate mofetil, mizoribine, 15-deoxyspergualine, leflunomide, steroids, cyclophosphamide, azathioprene (AZA), or anti-lymphocyte antibodies or immunotoxins such as monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, or CD25; especially in combination with a T-cell suppressant, e.g., cyclosporin A or FK-506. Such combination therapy is further comprised within the scope of the invention, e.g., a method according to 1 above further comprising administration concomitantly or in sequence of a therapeutically or synergistically effective amount of such a second immunosuppressive or anti-inflammatory agent.

The following examples are offered as a way for illustration of this invention and not in a way of limitation.

Abbreviations used: BnBr: benzyl bromide; CSA: camphorsulfonic acid; DCM: dichloromethane; DEAD: diethylazodicarboxylate; C-DHAP: 3-keto-4-hydroxy-butanyl-1-phosphonate; DHAP: dihydroxyacetone phosphate; dppb: 1,4-bis(diphenylphosphino)butane; DMAP: 4-dimethylaminopyridine; DMF: dimethylformamide; DMS: dimethylsulfide; EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; ESI: electrospray ionization; HOBt: 1-hydroxybenzotriazole; HOSu: N-hydroxy succinimide; NBA: m-nitrobenzylalcohol; NMM: 4-methyl morpholine; PPh_3: triphenylphosphine; RT: room temperature; SGCC: silica gel column chromatography; TBAF: tertbutylammonium fluoride; TBAI: tetrabutylammonium iodide; THF: tetrahydrofuran; TMSOTf: trimethylsilyltriflate

Examples

General procedures

Hydrogenation of Mannose Based Mimetics: To a stirred solution of the amide in 2 ml of HOAc is added 2 drops of H_2O, a catalytic amount of 10% Pd/C and H_2 gas. After stirring for 1 day, the catalyst is filtered off through a pad of celite and the pad is rinsed with HOAc. The filtrate is concentrated under reduced pressure to provide a white solid or a colorless oil. After lyophilization this product is a white hygroscopic solid.

Coupling a Carboxylic Acid and an Amine: To a stirred 0°C solution of the carboxylic acid (1.0 mmol), HOBt (1.2 mmol), the amine (2.0 mmol) and NMM (2.5 mmol) in CH_2Cl_2 [0.5 M] is added EDC (1.3mmol). After stirring overnight and subsequent warming to RT, tlc analysis indicates complete consumption of the starting acid. Sat. $NaHCO_3$ soln. and CH_2Cl_2 are added to the reaction mixture. The aqueous portion is extracted twice with CH_2Cl_2. The

combined organic fractions are washed with 1N HCl and brine, dried over Na_2SO_4 and concentrated. The crude residue is purified by flash chromatography in silica gel using ethyl acetate/hexane as the eluent.

Removal of Boc Group: The Boc compound (1.0 mmol) is dissolved in a 50:50 mixture of CH_2Cl_2:TFA and the mixture is cooled to 0°C. After 30 min, tlc analysis indicates the complete consumption of the starting material. The residue is concentrated to remove the excess TFA and CH_2Cl_2 and the residue is rinsed with $CHCl_3$ and concentrated to remove any traces of TFA. The TFA amine salt is the one used in the general procedure for coupling a carboxylic acid and an amine, using an additional equivalent of NMM.

Succinate Anhydride Coupling: To a stirred solution of succinic anhydride (1.0 mmol; alternatively can use glutaric anhydride) and amine (1.1 mmol) in methylene chloride (0.5 M) is added NMM (1.1 mmol). After stirring overnight, the reaction is quenched with brine and methylene chloride. Aqueous portion is extracted with methylene chloride. Combined organics are dried with sodium sulfate and concentrated. The crude residue is purified by flash chromatography on silica gel using ethylacetate/hexanes as the solvent mixture.

Asymmetric dihydroxylation (AD-reaction). The diols are prepared from the unsaturated esters according to the literature protocol as follows: A solution of AD-mix (α or β) (1.4 g/mmol olefin) in tert.-butanol (5 ml) and H_2O (5 ml) is cooled to 0°C, $MeSO_2NH_2$ and the olefin (1 mmol) are added and the heterogeneous mixture is stirred at 4°C until completion is indicated by tlc (up to 48 h, to avoid very slow conversion, addition of extra potassium osmate (1.3 mg) is recommended). Sodium sulfite (1.5 g) is added at 4°C and stirring is continued at 23°C for 30 min. Triple extraction with EtOAc is followed by washings with 1 N NaOH and brine. After drying over Na_2SO_4 and removal of the solvent in vacuo the residual slightly yellow solid is purified by SGCC (gradient elution EtOAc in hexanes) to give the desired diol.

Peptide coupling with EDC/HOBt: GP A: A solution of the amine, HOBt, the carboxylic acid and NMM in dry DMF is cooled to -20°C and EDC is added in one portion. The reaction mixture is stirred at -20°C for 1 h and then allowed to reach 23°C slowly. After 16 to 36 h the reaction is taken up in ethyl acetate and extracted with 5% w/v citric acid solution (20 ml). The aqueous layer is further extracted with ethyl acetate (4 x 20 ml) and the combined organic layers are washed with sat. $NaHCO_3$-sol. (40 ml) and brine (40 ml) followed by drying over $MgSO_4$. After evaporation under reduced pressure the residual oil is purified by

silica gel column chromatography (gradient elution with 30%→100% EtOAc in hexanes) to give the coupled compound.

GP B: A solution of the amine, HOBt, the carboxylic acid and NMM in dry CH_2Cl_2 is cooled to 0°C and EDC is added in one portion. The reaction mixture is stirred several h at 0°C and then allowed to reach 23°C slowly. After 4 to 18 h the reaction is worked up as described above in GP A.

Final deprotection by hydrogenolysis: GP A: A solution of the benzyl protected compound in 80% aq. HOAc is hydrogenated at 1 atm in the presence of Pd/C (10% Pd on activated carbon) at 23°C overnight. The reaction is filtered through celite, washed with H_2O and the solvent is removed under reduced pressure. An aqueous solution of the residue is either directly filtered through a Whatman® Anotop inorganic membrane filter (Anotop 25 (0.2 µm) or Anotop 10 (0.02 µm)) or, if necessary, purified by Biogel P2 or Sephadex G10 column chromatography (H_2O as eluent) and lyophilized to give the completely deprotected compound as a white solid.

GP B: A solution of the benzyl protected compound in EtOH/H_2O (2:1) is hydrogenated at 1 atm in the presence of $Pd(OH)_2$/C (Degussa type, 20% $Pd(OH)_2$ on activated carbon) for several hours. The reaction is worked up as described above in GP A.

Coupling procedures for the synthesis of compounds of group (d) wherein R^2 is OH, Y' is CH_2 and $R^{2'}$ is $C(O)NHCHR^4C(O)OH$: A solution of 1.1 equivalents protected amino acid with a free amine, wherein, the protected amino acid is selected from the group consisting of Ala-OBn • pTSOH, Val-OBn • pTSOH, Leu-OBr • pTSOH, Ile-OBn • pTSOH, Pro-OBn • pTSOH, Phe-OBn • pTSOH, Trp-OBn • pTSOH, Met-OBn • pTSOH, Ser-OBn • pTSOH, Thr-OBn • pTSOH, Cys-OBn • pTSOH, Tyr-OBn • pTSOH, Asn-OBn • pTSOH, Gln-OBn • pTSOH, Asp-$(OBn)_2$ • pTSOH, Glu-$(OBn)_2$ • pTSOH, Gly-OBn • pTSOH, Lys-OBn • pTSOH, Arg-OBn • pTSOH, and His-OBn • pTSOH (D- and L-amino acids; HCl salt may be used in lieu of the TSOH salt; other protecting groups in lieu of benzyl ether may be used), 1.1 equivalents HOBt, 1.0 equivalents of **108(3)** and 1.1 equivalents of NMM in dry 0.15 M DMF is cooled to -20°C and 1.1 equivalents of EDC are added in one portion. The reaction mixture is stirred at -20°C for 1 hour and then allowed to reach 23°C slowly. After 16 to 36 h the reaction is taken up in ethyl acetate and extracted with 5% w/v citric acid solution (20 ml). The aqueous layer is further extracted with ethyl acetate (4 x 20 ml) and the combined organic layers are washed with sat. $NaHCO_3$-sol. (40 ml) and brine (40 ml) followed by drying over $MgSO_4$. After evaporation under reduced pressure the residual oil is purified by

SGCC (gradient elution with 30%→100% EtOAc in hexanes) to give the coupled protected mimetic.

Alternatively (same equivalents as above), the solution of the amino acid, HOBt, **108(3)** and NMM in dry CH_2Cl_2 is cooled to 0°C and EDC is added in one portion. The reaction mixture is stirred several h at 0°C and then allowed to reach 23°C slowly. After 4 to 18 h the reaction is worked up as described above.

Deprotection procedures for the above compounds: A solution of 1.1 equivalents of the benzyl protected mimetic (supra) in 80% aq. acetic acid is hydrogenated at 1 atm in the presence of a catalytic amount of Pd/C (10% Pd on activated carbon; approx. 0.5 equivalents) at 23°C overnight. The reaction is filtered through celite, washed with H_2O and the solvent is removed under reduced pressure. An aqueous solution of the residue is either directly filtered through a Whatman® Anotop inorganic membrane filter (Anotop 25 (0.2 µm) or Anotop 10 (0.02 µm)) or, if necessary, purified by Biogel P2 or Sephadex G10 column chromatography (H_2O as eluent) and lyophilized to give the completely deprotected compound as a white solid.

Alternatively, a solution of the benzyl protected compound (supra) in 0.10 M EtOH/H_2O (2:1) is hydrogenated at 1 atm in the presence of $Pd(OH)_2/C$ (Degussa type, 20% $Pd(OH)_2$ on activated carbon; catalytic amount approx. 0.5 equivalents) for several hours. The reaction is worked up as described above.

Coupling procedures for the synthesis of compounds of group (d) wherein R^2 is OH, Y' is alkylene substituted with one or two OH and $R^{2'}$ is C(O)NHCHR^{4}C(O)OH: Starting from a solution of 1.1 equivalents protected amino acid with a free amine as mentioned above, 1.1 equivalents HOBt), 1.0 equivalents carboxylic acid derived from **113(3)** and 1.1 equivalents NMM in dry 0.15 M DMF the coupled protected mimetics are prepared according to the procedure described above for the compounds of group (d) wherein R^2 is OH, Y' is CH_2 and $R^{2'}$ is C(O)NHCHR^{4}C(O)OH.

Deprotection procedures for the synthesis of the above compounds: The protected mimics above are deprotected as described above for the compounds of group (d) wherein R^2 is OH, Y' is CH_2 and $R^{2'}$ is C(O)NHCHR^{4}C(O)OH.

Reduction of the azides with PPh_3/H_2O: A solution of the azide (1 mmol) and PPh_3 (1.1 up to 2 mmol) in THF (0.2 M) and H_2O (21 µl) is stirred at 23°C for 2 up to 7 days. The reaction mixture is concentrated in vacuo and residual oil is purified by SGCC (gradient elution with the CH_2Cl_2:MeOH:NH_4OH solvent system) to give the desired amine.

Asymmetric dihydroxylation (AD-reaction): The diols are prepared from the unsaturated esters according to the literature protocol [Sharpless et al. J. Org. Chem. 57:2768-2771 (1992); Kolb et al. Chem. Rev. 94:2483-2547 (1994)] as follows: A solution of AD-mix (α or β) (1.4 g/mmol olefin) in tert.-butanol (5 ml) and H_2O (5 ml) is cooled to 0°C, $MeSO_2NH_2$ and the olefin (1 mmol) are added and the heterogeneous mixture is stirred at 4°C until completion is indicated by tlc (up to 48h, to avoid very slow conversion, addition of extra potassium osmate (1.3 mg) is recommended). Sodium sulfite (1.5g) is added at 4°C and stirring is continued at 23°C for 30min. Triple extraction with EtOAc is followed by washings with 1N NaOH and brine. After drying over Na_2SO_4 and removal of the solvent in vacuo the residual slightly yellow solid is purified by SGCC (gradient elution EtOAc in hexanes) to give the desired diol.

Peptide coupling with EDC/HOBt - Procedure A: A solution of the amine, HOBt, the carboxylic acid and NMM in dry DMF is cooled to -20°C and EDC is added in one portion. The reaction mixture is stirred at -20°C for 1h and then allowed to reach 23°C slowly. After 16 to 36 h the reaction is taken up in ethyl acetate and extracted with 5% w/v citric acid solution (20 ml). The aqueous layer is further extracted with ethyl acetate (4 x 20 ml) and the combined organic layers are washed with sat. $NaHCO_3$-sol. (40 ml) and brine (40 ml) followed by drying over $MgSO_4$. After evaporation under reduced pressure the residual oil is purified by SGCC (gradient elution with 30%→100% EtOAc in hexanes) to give the coupled compound.

Procedure B: A solution of the amine, HOBt, the carboxylic acid and NMM in dry CH_2Cl_2 is cooled to 0°C and EDC is added in one portion. The reaction mixture is stirred several h at 0°C and then allowed to reach 23°C slowly. After 4 to 18h the reaction is worked up as described above in Procedure A.

Removal of the Boc protecting group: A solution of the Boc peptide in dry $CHCl_3$ (1 ml) is treated with TFA (1 ml) at 0°C and stirred for 90 min. slowly reaching 23°C. The reaction mixture is evaporated under reduced pressure, twice $CHCl_3$ (15 ml) is added and the solvent is removed in vacuo. The residual oil is taken up in MeOH (10 ml) and Dowex 1X8-50 OH resin is added until pH 8 is reached. The resin is filtered off, washed with MeOH, the solvent is removed in vacuo and the residue is used in the next step without further purification.

Introduction of the diacid moiety via activated esters: A solution of the amine in $CHCl_3$ or a mixture of $CHCl_3$ or CH_2Cl_2 and DMF is cooled to 0°C and the succinimide ester [The

monobenzyl N-succinimidyl glutarate and the corresponding succinate are prepared according to the following protocol: i) glutaric or succinic anhydride, BnOH, $CHCl_3$, pyridine, DMAP, 50°C; ii) HOSu, EDC, DCM. The latter step from: Spevak et al. J. Am. Chem. Soc. 115:1146-1147 (1993)] is added in one portion. If the TFA salt of the amine is employed the reaction mixture is treated with NMM until a basic pH is achieved. The reaction mixture is stirred at 0°C for several h and then allowed to reach 23°C slowly. After 16 to 36h the reaction is taken up in ethyl acetate and extracted with 5% w/v citric acid solution (20 ml). The aqueous layer is further extracted with ethyl acetate (4 x 20 ml) and the combined organic layers are washed with sat. $NaHCO_3$-sol. (40 ml) and brine (40 ml) followed by drying over $MgSO_4$ or Na_2SO_4 in the case of unprotected diols. After evaporation under reduced pressure the residual oil is purified by SGCC (gradient elution with 40%→100% EtOAc in hexanes) to give the coupled compound.

A Preparation of the starting compounds

Example A1: Preparation of compound (19)

(a) Synthesis of 1,2-epoxy-3-(tri-O-benzyl-α-L-fucopyranosyl) propane (18): A solution of 3-(tri-O-benzyl-α-L-fucopyranosyl)-1-propene 17 [Uchiyama et al. Bioorg. Med. Chem. 4:1149-1165 (1996)] (7.0g, 15.3 mmol) in CH_2Cl_2 (70 ml) is cooled to 0°C and mCPBA (8.5g, ca. 25 mmol, ca. 50% w/w) is added followed by stirring at 23°C for 11h. The reaction is quenched with icewater, taken up in ether and the excess mCPBA is destroyed with Na_2SO_3 in sat. $NaHCO_3$-sol. The organic layer is extracted twice with sat. $NaHCO_3$, treated with brine and dried over $MgSO_4$. Removal of the solvent in vacuo left a yellow oil, which is purified by SGCC (gradient elution 20%→35% EtOAc in hexanes) to yield 18 as a colorless oil (1:1 diastereomeric mixture).

(b) Synthesis of 1-azido-3-(tri-O-benzyl-α-L-fucopyranosyl)-2-propanol (19): To a solution of 18 (5.90g, 12.4 mmol) in EtOH/H_2O (9:1, 25 ml) is added NaN_3 (4.04g, 62.2mmol) and NH_4Cl (3.32 g, 62.2mmol) and the resulting suspension is heated to reflux for 1.5h. After reaching 23°C, the reaction is taken up in ether, washed with H_2O, brine and dried over $MgSO_4$. Removal of the solvent in vacuo leaves a yellow oil, which is purified by SGCC (gradient elution 20%→33% EtOAc in hexanes) to yield 19 as a yellow oil (1:1 diastereomeric mixture). Separation of the diastereomers is performed by HPLC on a semipreparative column with hexane/2-propanol 99.5:0.5 at a flow rate of 9 ml/min.

Example A2: Preparation of compound (25)

(a) Synthesis of 1-azido-2-(2-phenethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (20): A biphasic solution of 19b (207 mg, 400 µmol) in 2-bromoethylbenzene (3 ml) and 50 % aqueous NaOH-solution (2 ml) is stirred for 5 days at 23°C in the presence of n-Bu_4NHSO_4 (22 mg, 65 µmol). The reaction is diluted with Et_2O, washed with H_2O, 5 % citric acid, sat. $NaHCO_3$-sol. and brine, followed by drying over $MgSO_4$. The solvent is removed in vacuo and the remaining oil is purified by SGCC (0%→10%→20%→50% EtOAc in hexanes) to yield 20b as a yellow oil. The corresponding diastereomer 20a is obtained similarly by treatment of 19a (281mg, 543µmol) in 2-bromoethylbenzene (4.1 ml) and 50 % aq. NaOH-sol. (2.7 ml) in the presence of n-Bu_4NI (30 mg, 81 µmol) and n-Bu_4NHSO_4 (30mg, 88µmol) for 10 days at 23°C to afford 20a as a yellow oil.

(b) Synthesis of 2-(2-phenethoxy)-2-(tri-O-benzyl-α-L-fucopyranosyl)-1-propyl amine (23): A solution of 20a (29.1 mg, 46.8 µmol) in THF (0.5 ml) and H_2O (1 drop) is treated with PPh_3 (15mg, 57.2µmol) according to the general procedure for 2.5 days at 23°C to give amine 23a as a colorless oil. The corresponding diastereomer 23b is obtained similarly by treatment of 20b (46 mg, 74 µmol) in THF (0.5 ml) and H_2O (1 drop) with PPh_3 (24 mg, 91.5 µmol) for 1.25 days at 23°C to afford amine 23b as a colorless oil.

(c) Synthesis of 1-(O-benzyl-N-tert.-butoxycarbonyl-L-threonine)-2-(2-phenethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (24): A solution of 23a (24mg, 40.3µmol), EDC (9.4mg, 49.0µmol), HOBt (6.6mg, 48.8 µmol), N-Boc-O-benzyl-L-threonine (14.4mg, 46.5µmol) and NMM (10µl, 91µmol) in dry DMF (0.7 ml) is coupled according to the general procedure (GP A) for 51h to give 24a as a white solid. The corresponding diastereomer 24b is obtained similarly, by treatment of 23b (35.7 mg, 59.9µmol) with EDC (13.8 mg, 72.0 µmol), HOBt (9.8mg, 72.5µmol), N-Boc-O-benzyl-L-threonine (22.0 mg, 71.1µmol) and NMM (15µl, 136µmol) in dry DMF (1.0ml) according to the general procedure for 21h to give 24b as a white solid.

(d) Synthesis of 1-(3-O-benzyl-2-monobenzyl-succinamidyl-L-threonine)-2-(2-phenethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (25): According to the general procedure Boc carbamate 24a (34.9 mg, 39µmol) is deprotected and coupled with monobenzylsuccinate (11.7mg, 56.2µmol), EDC (11.4mg, 59.5µmol), HOBt (8.6mg, 63.6µmol) and NMM (11µl, 100µmol) in dry DMF (0.9 ml) for 33h to give 25a (37.0mg, 98%) as a white solid. The

corresponding diastereomer 25b is obtained similarily by deprotection of Boc carbamate 24b (44.7mg, 50.4µmol) and subsequent coupling with monobenzylsuccinate (12.1mg, 58.1µmol), EDC (14.8mg, 77.2µmol), HOBt (9.1mg, 67.3µmol) and NMM (12µl, 129µmol) for 38h to afford 25b as a white solid.

Example A3: Preparation of compound (26)

(a) Synthesis of 1-azido-2-(3-phenyl-2-propenoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (21): To a solution of 19 (400 mg, 773 µmol) in THF (5ml) and DMF (0.9 ml) is subsequently added NaH (95%) (56mg, 2.33 mmol) and cinnamyl bromide (309 mg, 1.57 mmol). The mixture is heated to 65°C for 1h, cooled to 23°C, diluted with Et_2O, washed with H_2O and brine, followed by drying over $MgSO_4$. The solvent is removed in vacuo and the remaining oil is purified by SGCC (15%→18% EtOAc in hexanes) to yield 21 as a yellow oil (1:1 diastereomeric mixture).

(b) Synthesis of N-(tert.-butoxycarbonyl)-2-(3-phenylpropoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)-1-propyl amine (26): A solution of 21 (343 mg, 541µmol) and Boc_2O (149mg, 683µmol) in EtOAc (6.1ml) is stirred in the presence of Pd/C (16.5mg, 10% Pd on activated carbon) for 2 days at 23°C under atmospheric hydrogen pressure. The catalyst is filtered off through celite, washed with EtOAc, the solvent is removed in vacuo and the remaining oil is purified by SGCC (16%→18%→20%→33% EtOAc in hexanes achieves separation of the two diastereomers) to give Boc-carbamate 26 as a pale yellow oil.

Example A4: Preparation of compound (28b)

(a) Synthesis o(2*S*)-1-{(2*S*,3*R*)-4-benzyloxy-2-(tert-butoxycarbonylamino)-3-hydroxybutyramidyl}-2-(3-phenylpropoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)-propane (27b): According to the general deprotection procedure Boc-carbamate 26b (128 mg, 180 µmol) is deprotected and subsequently coupled to (2*S*,3*S*)-4-benzyloxy-2-tert.-butoxycarbonylamino-2-hydroxy-butanoic acid **16a** (70 mg, 215 µmol) by treatment with EDC (42 mg, 219 µmol), HOBt (30 mg, 222 µmol) and NMM (25 µl, 227 µmol) in DCM (2.0 ml) for 5.5 h to yield 27b as a yellow oil.

(b) Synthesis of (2*S*)-1-{(2*S*,3*R*)-4-benzyloxy-2-(benzylsuccinamidyl-3-hydroxybutyramidyl)-2-(3-phenylpropoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)-propane (28b): According to the general procedure Boc-carbamate 27b (103 mg, 112 µmol) is deprotected and subsequent-

ly coupled to monobenzyl succinate (26.6 mg, 128 µmol) by treatment with EDC (25 mg, 130 µmol), HOBt (18.2mg, 135 µmol) and NMM (26 µl, 236 µmol) in DCM (1.1 ml) for 4h to yield 26b as a yellow oil.

Example A5: Preparation of compound (32b)

(a) Synthesis of 1-azido-2-(tert.-butoxycarbonylmethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)-propane (22): A biphasic solution of 19a/19b (ca. 1.3) (706 mg, 1.36 mmol), tert.-butyl-bromoacetate (2.0 ml, 13.6 mmol), toluene (2.8 ml) and 50 % aqueous NaOH-solution (2 ml) is stirred for 2 days at 4°C in the presence of n-Bu_4NHSO_4 (46 mg, 136 µmol). The reaction is diluted with Et_2O, washed with H_2O, 5 % citric acid, sat. $NaHCO_3$-sol. and brine, followed by drying over $MgSO_4$. The solvent is removed in vacuo and the remaining oil is purified by SGCC (20% EtOAc in hexanes) to yield 22 as a slightly yellow oil (diastereomeric ratio 22a/22b ca. 1:3).

(b) Synthesis of 1-amino-2-(tert.-butoxycarbonylmethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (29): Azide 22 (240 mg, 0.38 mmol) is treated with PPh_3 (120 mg, 0.46 mmol) in THF (2.2 ml) and H_2O (2 drops) for 3 days according to the general procedure to give 29 as a colorless oil (diastereomeric ratio 29a/29b ca. 1:3).

(c) Synthesis of 1-(O-benzyl-N-tert.-butoxycarbonyl-L-threonine)-2-(tert.-butoxycarbonyl-methoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (30): A solution of 29 (112.5 mg, 186 µmol), EDC (40.8 mg, 213 µmol), HOBt (29.4 mg, 218 µmol), N-Boc-O-benzyl-l-threonine (64.2 mg, 207 µmol) and NMM (45 µl, 409 µmol) in dry DMF (3.0 ml) is coupled according to the general procedure for 51h to give 30 as a colorless oil. Separation by SGCC (30%→-40%→50% EtOAc in hexanes) of the diastereomers affords 30b as a white solid.

(d) Synthesis of (2*S*)-1-(3-O-benzyl-2-monobenzyl-succinamidyl-L-threonine)-2-(carboxyl-methoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (31b): According to the general deprotection procedures Boc carbamate and tert.-butyl ester 30b (87.5 mg, 97.5 µmol) are simultaneously deprotected (10.5h) and the resulting TFA-salt is treated with $BnO_2C(CH_2)_2CO_2Su$ (40 mg, 131 µmol) and NMM (60 µl, 546 µmol) in dry DMF (2.2 ml) for 18h to give 31b as a colorless oil. In this case the workup procedure is changed to EtOAc as extracting solvent and consecutive washings with 1N HCl and brine, followed by drying over $MgSO_4$ to assure isolation of the carboxylic acid, which is chromatographed on silica gel (DCM:MeOH:HOAc 29:1:0.1→19:1:0.1).

(e) Synthesis of (2*S*)-1-(3-O-benzyl-2-monobenzyl-succinamidyl-L-threonine)-2-(tetradecyl-aminocarbonylmethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (32b): According to the general coupling procedure B carboxylic acid 31b (3.5 mg, 46.7 µmol) is coupled with tetradecyl amine (11.1 mg, 52.0 µmol) using EDC (11.0 mg, 57.4 µmol) and NMM (11 µl, 102 µmol) in $CHCl_3$ (0.7 ml) for 26h to give 32b as a yellow oil.

Example A6: Preparation of compound (34b)

(a) Synthesis of (2*S*)-1-(3-O-benzyl-2-monobenzyl-succinamidyl-L-threonine)-2-(serinol-carbonylmethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (33b): According to the general procedure A carboxylic acid 31b (45.1 mg, 48.4 µmol) and serinol (5.8 mg, 63.7 µmol) are coupled using EDC (13.7 mg, 71.5 µmol), HOBt (9.3 mg, 68.8 µmol) and NMM (13 µl, 118 µmol) in dry DMF (1.0 ml) for 12h to give 33b as a colorless oil (SGCC with DCM/MeOH 9:1).

(b) Synthesis of (2*S*)-1-(3-O-benzyl-2-monobenzyl-succinamidyl-L-threonine)-2-(dimyristoyl-serinolcarbonylmethoxy)-3-(tri-O-benzyl-α-L-fucopyranosyl)propane (34b): To a solution of diol 33b (30.1 mg, 30.0 µmol) and pyridine (60 µl, 742 µmol) in dry DCM (0.45 ml) is added freshly distilled myristoyl chloride (49 µl, 180 µmol) at 23°C and the mixture is stirred for 4.5h. After dilution with DCM, the organic layer is successively washed with 1 N HCl-sol., sat. $NaHCO_3$-sol. and brine, followed by drying over $MgSO_4$. Removal of the solvent in vacuo gives a yellow oil, which is purified by SGCC (66% EtOAc in hexanes) to afford 34b as a colorless oil.

Example A7: Preparation of compound (37)

(a) Synthesis of N-tert.-butoxycarbonyl-N-(methoxycarbonylmethyl)-2-(tri-O-benzyl-α-L-fuco-pyranosyl)ethyl amine (36): A solution of 2-(tri-O-benzyl-α–L-fucopyranosyl)-acetaldehyde 35 (724mg, 1.57mmol), synthesized according to the procedure of Uchiyama et al [Bioorg. Med. Chem. 4:1149 (1996)], glycine methyl ester hydrochloride (197.4 mg, 1.57 mmol), Et_3N (0.44 ml, 3.14mmol) and $MgSO_4$ (132.4 mg, 1.1mmol) in dry CH_2Cl_2 (3.3 ml) is stirred at 23°C for 13h. The solid remains are filtered off, washed with dry CH_2Cl_2 and the solvent is removed in vacuo. The imine produced is dissolved in dry MeOH (9ml) and cooled to 0°C, whereas $NaBH_4$ (150mg, 3.9 mmol) is added in one portion. After 20 min. the reaction mixture is concentrated under reduced pressure and the remaining oil is coevaporated with

CH_2Cl_2 (25ml) to remove the rest MeOH. The residue is dissolved in CH_2Cl_2 (15ml) and Boc_2O (795mg, 3.6 mmol) is added at 0°C. The reaction is warmed up to 23°C and stirred for 50 min. After diluting with Et_2O, the organic layer is washed with 5%w/v citric acid sol., sat. $NaHCO_3$-sol. and brine, followed by drying over $MgSO_4$. The solvent is removed in vacuo and the remaining oil is purified by SGCC (gradient elution 20%→30%→35%→40% EtOAc in hexanes) to give 36 as a colorless oil.

(b) Synthesis of N-tert.-butoxycarbonyl-N-(carboxylmethyl)-2-(tri-O-benzyl-α-L-fucopyranosyl)ethyl intermediate amine: A solution of methyl ester 36 (600mg, 0.95mmol) in THF (4.5ml) is treated with LiOH (19ml, 0.25m solution in MeOH/H_2O 3:1) and stirred at 4°C for 42h. The solution is acidified with 1N HCl-sol. until pH 1-2 is reached and extracted with EtOAc, washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo affords the title acid as a colorless foam.

(c) Synthesis of N-tert.-butoxycarbonyl-N-(tetradecylaminocarboxylmethyl)-2-(tri-O-benzyl-α-L-fucopyranosyl)ethyl amine intermediate: According to the general procedure the above acid (225 mg, 363 µmol) is coupled with tetradecyl amine (85 mg, 398 µmol) using EDC (76.5mg, 399µmol) and NMM (84µl, 764µmol) in $CHCl_3$ (3.5ml) for 2.5 days to give the title amide as a slightly yellow oil.

(d) Synthesis of N-(tetradecylaminocarboxylmethyl)-2-(tri-O-benzyl-α-L-fucopyranosyl)ethyl amine (37): According to the general deprotection procedure the above Boc carbamate (205mg, 252µmol) is deprotected to give 37 as a slightly yellow oil.

Example A8: Preparation of compound (16)

(a) Ethyl (E)-ω-benzyloxy-2-alkenoate (11): Prepared from the corresponding ω-benzyloxy-alkanal 10 according to Blanchette et al. [Tetrahedron Lett. 2183-2186 (1984)] as follows: To a suspension of LiCl (12 mmol) and triethyl phosphonoacetate (12 mmol) in dry CH_3CN (100 ml) is added DBU (10 mmol) followed by the aldehyde **10** Bn-O-$(CH_2)_{1-3}$-CHO (10 mmol) at 23°C and the reaction is stirred for ca. 4h. The mixture is taken up in ether, extracted with 1N HCl, sat. $NaHCO_3$-sol. and brine, dried over $MgSO_4$. After removal of the solvent in vacuo the residue is purified by SGCC (15% EtOAc in hexanes) to give the ethyl (E)-ω-benzyloxy-2-alkenoate 11 as a yellow oil. Ethyl (*E*)-4-benzyloxy-2-butenoate (11a); ethyl (*E*)-5-benzyloxy-2-pentenoate (11b); ethyl (*E*)-6-benzyloxy-2-hexenoate (11 c).

(b) Synthesis of ethyl ω-benzyloxy-cis-2,3-dihydroxyalkanoate (12): Prepared from the unsaturated ester according to the general procedure to give 12 as a colorless solid. Ethyl (2*R*,3*R*)-4-benzyloxy-2,3-dihydroxybutanoate (12a); ethyl (2*R*,3*S*)-5-benzyloxy-2,3-dihydroxypentanoate (12b); ethyl (2*R*,3*S*)-6-benzyloxy-2,3-dihydroxyhexanoate (12c).

(c) Ethyl ω-benzyloxy-cis-3-hydroxy-2-(4-nitrobenzenesulfonyloxy)alkanoate (13): Prepared from diol 12 according to Sharpless et al. [J. Org. Chem. 56:2869-2875 (1991)] as follows: A solution of diol 12 (5 mmol) in dry pyridine (17 ml) is cooled to 0°C and 4-nitrobenzenesulfonyl chloride (5.05 mmol, freshly recrystallized from hexane) is added. After standing for 24-30h at 4°C the mixture is poured into ice and extracted with ether. After multiple washings with sat. $CuSO_4$-sol., one washing with brine and drying over $MgSO_4$, the solvent is removed in vacuo. The residual oil is purified by SGCC (30%→40% EtOAc in hexanes) to give the 2-nosylate 13 as a yellow oil. Ethyl (2*R*,3*R*)-4-benzyloxy-3-hydroxy-2-(4-nitrobenzene-sulfonyloxy)-butanoate (13a); ethyl (2*R*,3*S*)-5-benzyloxy-3-hydroxy-2-(4-nitrobenzenesulfonyloxy)pentanoate (13b).

(d) Ethyl trans-2-azido-ω-benzyloxy-3-hydroxyalkanoate (14): Prepared from nosylate 13 according to Sharpless et al. [J. Org. Chem. 56: 2869 (1991)] as follows: A solution of nosylate 13 (5 mmol) and sodium azide (30 mmol) in dry DMF (50 ml) is stirred at 50°C for 14 h. The reaction mixture is poured into ice water and extracted three times with ether. The combined organic layers are washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo the residue is purified by SGCC (30%→40% EtOAc in hexanes) to give azide 14 as a slightly yellow oil. Ethyl (2*S*,3*R*)-2-azido-4-benzyloxy-3-hydroxybutanoate (14a), ethyl (2*S*,3*R*)-2-azido-5-benzyloxy-3-hydroxybutanoate (14b).

(e) Synthesis of ethyl trans-ω-benzyloxy-2-tert.-butoxycarbonylamino-3-hydroxyalkanoate (15): A solution of azide 14 (1 mmol) and Boc_2O (1.2 mmol) in EtOAc (15 ml) is hydrogenated in the presence of Rh/C (30 mg, 5% Rh on activated carbon) at atmospheric pressure under vigorous stirring for 7 h at 23°C. The reaction mixture is filtered through a celite pad and washed with EtOAc. The solvent is removed in vacuo and the residue is purified by SGCC (30% EtOAc in hexanes) to give 15 as a colorless oil. Ethyl (2*S*,3*R*)-4-benzyloxy-2-tert.-butoxycarbonylamino-3-hydroxybutanoate (15a); ethyl (2*S*,3*S*)-5-benzyloxy-2-tert.-butoxycarbonylamino-2-hydroxypentanoate (15b).

(f) Synthesis of trans-ω-benzyloxy-2-tert.-butoxycarbonylamino-3-hydroxyalkanoic acid (16): An ice-cold solution of LiOH (20 ml, 0.25 M in MeOH/H_2O 3:1) is added to ethyl ester 15 (1 mmol) at 0°C and vigorous stirring is continued for 2 days at 4°C. The reaction mixture is

acidified with cold 1 N HCl to pH 1-2 and quickly extracted with EtOAc, washed with brine and dried over $MgSO_4$. The solvent is removed in vacuo to give acid (16) as a slightly yellow oil. (2*S*,3*S*)-4-Benzyloxy-2-tert.-butoxycarbonylamino-2-hydroxybutanoic acid (16a); (2*S*,3*S*)-5-benzyloxy-2-tert.-butoxycarbonylamino-2-hydroxypentanoic acid (16b).

Example A9: Preparation of compound 39

(a) Synthesis of 1-{(2*S*,3*R*)-4-benzyloxy-2-(tert-butoxycarbonylaminio)-3-hydroxybutyramidyl}-N-(tetradecylaminocarbonylmethyl)-2-(tri-O-benzyl-α-L-fucopyranosyl)-ethane **38**: According to the general procedure A amine **37** (103mg, 140µmol) is coupled to **16a** (53mg, 163µmol) by treatment with EDC (32mg, 167µmol), HOBt (29mg, 215µmol) and NMM (35µl, 318µmol) in DMF 81.3ml) for 40h to yield **38** as a yellow oil.

(b) Synthesis of 1-{(2*S*,3*R*)-2-benzylglutaramidyl-4-benzyloxy-3-hydroxybutyramidyl}-N-(tetradecylaminocarbonylmethyl)-2-(tri-O-benzyl-α-L-fucopyranosyl)-ethane **39**: According to the general deprotection procedures Boc-carbamate **38** (88mg, 86µmol) is deprotected and subsequently coupled with monobenzyl N-succinimidyl glutarate (34mg, 106µmol) in DCM (1.5ml) in the presence of NMM (6µl) for 8h to obtain **39** as a yellow oil.

Example A9': Preparation of compound (47)

(a) Synthesis of ethyl (*E*)-4-(tri-O-benzyl-α-L-fucopyranosyl)-2-butenoate (40): Prepared from the 2-(tri-O-benzyl-α-L-fucopyranosyl)-acetaldehyde 35 (synthesized according to the procedure of Uchiyama et al [Bioorg. Med. Chem. 4:1149 (1996)] according to Blanchette et al. [Tetrahedron Lett. 2183 (1984)] as follows: To a suspension of LiCl (215mg, 5.07mmol) and triethyl phosphonoacetate (1.00ml, 5.04mmol) in dry CH_3CN (42ml) is added DBU (0.63 ml, 4.21 mmol) followed by the aldehyde 35 (1.94g, 4.21mmol) at 23°C and the reaction is stirred for 6h. The mixture is taken up in ether, extracted with 1N HCl, sat. $NaHCO_3$-sol. and brine, dried over $MgSO_4$. After removal of the solvent in vacuo the residue is purified by SGCC (20%→22% EtOAc in hexanes) to give the α,β-unsaturated ester 40 as a yellow oil.

(b) Synthesis of ethyl (2*R*,3*S*)-2,3-dihydroxy-4-(tri-O-benzyl-α-L-fucopyranosyl)-butenoate (41): Prepared from the α,β-unsaturated ester 40 (2.09g, 3.94mmol) according to the general asymmetric dihydroxylation procedure to give 41 as a colorless oil.

(c) Synthesis of ethyl (2*R*, 3*S*)-3-hydroxy-2-(4-nitrobenzenesulfonyloxy)-4-(tri-O-benzyl-α-L-fucopyranosyl)-butanoate (42): Prepared from diol 41 according to Sharpless et al. [J. Org.

Chem. 56:2869 (1991)] as follows: A solution of diol 41 (1.925g, 3.41mmol) in dry pyridine (11.4ml) is cooled to 0°C and 4-nitrobenzenesulfonyl chloride (773mg, 3.49mmol, freshly recrystallized from hexane) is added. After standing for 25h at 4°C the mixture is poured into ice and extracted with ether. After multiple washings with sat. $CuSO_4$-sol., one washing with brine and drying over $MgSO_4$, the solvent is removed in vacuo. The residual oil is purified by SGCC (30%→40%→50%→60% EtOAc in hexanes) to give the 2-nosylate 42 as a pale yellow foam.

(d) Synthesis of ethyl (2*S*,3*S*)-2-azido-3-hydroxy-4-(tri-O-benzyl-α-L-fucopyranosyl)-butanoate (43): Prepared from nosylate 42 according to Sharpless et al [J. Org. Chem. 56:2869 (1991)] as follows: A solution of nosylate 42 (1.97g, 2.63 mmol) and sodium azide (1.02g, 15.7mmol) in dry DMF (26ml) is stirred at 50°C for 21h. The reaction mixture is poured into ice water and extracted three times with ether. The combined organic layers are washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo the residue is purified by SGCC (30%→35% EtOAc in hexanes) to give 43 as a slightly yellow oil.

(e) Synthesis of ethyl (2*S*,3*S*)-2-azido-3-(3-phenyl-2-propenoxy)-4-(tri-O-benzyl-α-L-fucopyranosyl)-butanoate (44): Prepared from nosylate 42 according to Lakhmiri et al. Tetrahedron Lett. 30:4669-4672 (1989)] as follows: To a clear solution of tris(dibenzylideneacetone)-dipalladium(0) (dba_3Pd_2) (23mg, 25µmol) and dppb (43mg, 0.1mmol) is added a solution of 43 (590mg, 1.0mmol) and cinnamyl ethyl carbonate *(Cinnamyl ethyl carbonate is prepared as follows: To a solution of cinnamyl alcohol (1.00g, 7.45mmol) and pyridine (3ml, 37.1mmol) in DCM (12ml) is added ethyl chloroformate (1.07ml, 11.2mmol) at 0°C and the mixture is stirred while warming up to 23°C for 90 min. The reaction is taken up in ether, extracted with icewater, sat. $CuSO_4$-sol. (3x), brine and dried over $MgSO_4$. After removal of the solvent in vacuo the residual oil is purified by SGCC (hexanes: ether 4:1) to give the cinnamyl ethyl carbonate (1.47g, 96%) as a colorless oil)* (627mg, 3.0 mmol) in dry THF (26ml) at 23°C and the reaction is stirred at 65°C for 3h. The reaction mixture is concentrated in vacuo and the residue is purified by SGCC (15%→16%→20% EtOAc in hexanes) to give 44 as a yellow oil.

(f) Synthesis of ethyl (2*S*,3*S*)-2-(tert.-butoxycarbonylamino)-3-(3-phenylpropoxy)-4-(tri-O-benzyl-α-L-fucopyranosyl)-butanoate (45): A solution of azide 44 (260mg, 368µmol) and Boc_2O (100mg, 458µmol) in EtOAc (4.8ml) is stirred in the presence of Pd/C (11mg, 10% Pd on activated carbon) for 38h at 23°C under atmospheric hydrogen pressure. The catalyst is filtered off through celite, washed with EtOAc, the solvent is removed in vacuo and

the remaining oil is purified by SGCC (20% EtOAc in hexanes) to give 45 as a pale yellow oil.

(g) Synthesis of Compound 46: (step i) A solution of methyl ester 45 (600mg, 0.95mmol) in THF (4.5ml) is treated with LiOH (19ml, 0.25M solution in MeOH/H_2O 3:1) and stirred at 4°C for 42 h. The solution is acidified with 1 N HCl-sol. until pH 1-2 is reached and extracted with EtOAc, washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo affords the title acid. (step ii) According to the general procedure the above acid (225mg, 363µmol) is then coupled with tetradecyl amine (85mg, 398µmol) using EDC (76.5mg, 399µmol) and NMM (84µl, 764µmol) in $CHCl_3$ (3.5ml) for 2.5 days to give 46.

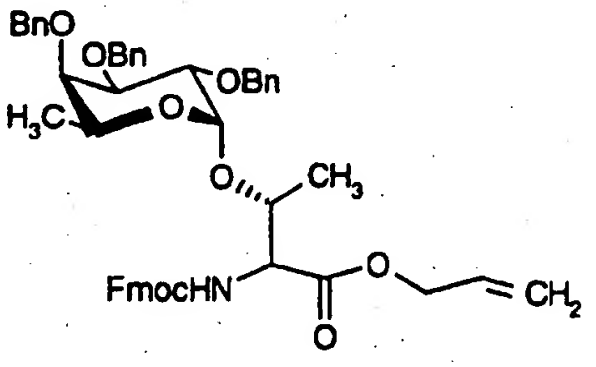
(h) Synthesis of Compound 47: (step i) According to the general deprotection procedure the above Boc carbamate 46 (205mg, 252µmol) is deprotected to give the intermediate amine (181mg, 99%) as a slightly yellow oil.

(step ii) According to the general procedure A amine from step i (103mg, 140µmol) is coupled to 16a (53mg, 163µmol) by treatment with EDC (32mg, 167µmol), HOBt (29mg, 215µmol) and NMM (35µl, 318µmol) in DMF (1.3ml) for 40h to yield the Boc-carbamate intermediate (89mg, 62%) as a yellow oil.

(steps iii-iv) According to the general deprotection procedures Boc-carbamate (88mg, 86µmol) is deprotected and subsequently coupled with monobenzyl n-succinimidyl glutarate (34mg, 106µmol) in DCM (1.5ml) in the presence of NMM (6µl) for 8h to obtain 47 as a yellow oil.

Example A10: Preparation of compound (54)

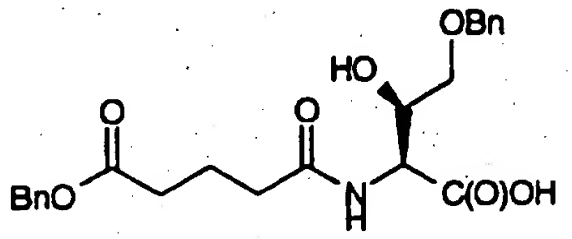
(a) Fmoc deprotection of compound **48**: A solution of compound **48**



[Wong et al. J. Am. Chem. Soc. 118:6826 (1996)] (411mg, 0.5mmole) in 40% $HNEt_2$/THF (10ml) is allowed to proceed at RT for 2h and is then evaporated in vacuo. The residue is

purified by flash column chromatography eluting with $CHCl_3$: MeOH (19:1) then (9:1) to afford **48'**.

(b) Coupling of **49** to fucosyl amine to form **50**: A mixture of **48'** (292 mg, 0.5 mmole), **49**



(218 mg, 0.5mmole) [Wong et al. Tetrahedron Lett. 36:4081 (1995)] and CH_2Cl_2 (6ml) is cooled to 0°C. The coupling reagent HOBT (89mg, 0.6 mmole) is added followed by EDC (127mg, 0.6mmole), and the solution is stirred at 0°C for 30 min. After being stirred at RT for 10h, the solvent is evaporated and the residue is diluted with EtOAc. The resulting organic layer is washed with H_2O (2x10ml), 1 N HCl (2x5ml), saturated aqueous $NaHCO_3$ (2x5ml), and saturated aqueous NaCl. The organic phase is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by flash column chromatography eluting with $CHCl_3$: MeOH (19:1) to afford **50** (395mg, 79%).

(c) Synthesis of **51**: To a solution of **50** (386mg, 0.4mmole) in 40ml of THF/DMF (1.1) is added tetrakis(triphenylphosphine)palladium(0) (45mg,0.04mmole) and morpholine (0.34ml, 4.0mmole). After stirred at RT for 11h, the solvent is evaporated and the residue is taken up in 50ml of EtOAc. The resulting solution is washed three times with 30ml of 1 N HCl, dried over $MgSO_4$, and concentrated in vacuo. The crude is purified by flash column chromatography eluting with $CHCl_3$: MeOH (9:1) to afford **51**.

(d) Synthesis of **53**: A mixture of $H_2N[(CH_2)_2O]_3(CH_2)_2N_3$ **52** (0.5 mmole; Toronto Research Chemicals Inc.), **51** (0.5 mmole) [Wong et al. Tetrahedron Lett 36:4081 (1995)] and CH_2Cl_2 (.068 M) is cooled to 0°C. The coupling reagent HOBT (0.6 mmole) is added followed by EDC (0.6 mmole), and the solution is stirred at 0°C for 30min. After being stirred at RT for 10h, the solvent is evaporated and the residue is diluted with EtOAc. The resulting organic layer is washed with H_2O (2x10ml, scaled accordingly, based on a 200-300mg scale for either substrate), 1 N HCl (2x5 ml), saturated aqueous $NaHCO_3$ (2x5 ml), and saturated aqueous NaCl. The organic phase is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by flash column chromatography eluting with $CHCl_3$: MeOH (19:1) to afford **53**.

(e) Preparation of **54**: **53** (256mg, 0.2 mmole) is dissolved in ethanol: H_2O: dioxane: AcOH (2:1:2:1, 2ml), and then a catalytic amount of $Pd(OH)_2$ (Degussa type; Aldrich) on carbon is

added. Hydrogen is supplied to the reaction system through a ballon. After 6h the mixture is filtered through celite and concentrated in vacuo. The crude product is purified by biogel P2 (water). The collected fractions are combined and freeze dried to afford **54**.

Example A11: Preparation of 57

Compound **55**  (1g, 2.7mmole; Avanti Polar Lipids, Inc.), HOSu (0.5g, 4.3mmole) and EDC (0.6g, 3.1mmole) are stirred in 65 ml of CH_2Cl_2 at RT while shielded from light. After 6 h, the solution is washed with water, 1% HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic phase is then dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield 57 as a slightly yellow solid.

Example A12: Preparation of D-mannose C-glycoside aldehyde 5(14)

(a) To a solution of methyl α-D-mannopyranoside (1.96 g, 9.61 mmol), BnBr (8 ml, 67.3 mmol), and TBAI (177 mg, 048 mol) in THF (20 ml) at 0°C is added NaH (2.35 g, 57.6 mmol). The cooling bath is removed and the reaction mixture is allowed to stir for 24 h. The reaction is diluted with EtOAc (50 ml). The aqueous phase is extracted with EtOAc (2x30ml) and the combined organic phases are dried ($MgSO_4$) and concentrated under reduced pressure providing the crude oil. Purification by silica gel flash chromatography (hexan:EtOAc, 100% to 9:1 to1:1) gives α-methyl-2,3,4,6-O-tetra-benzyl-mannopyranoside **2(14)**.

(b) To a solution of **2(14)** (1.0g, 2.56 mmol), at 0°C is added allyltrimethylsilane (1.22ml, 7.69mmol) followed by $BF_3 \cdot Et_2O$ (1.5ml, 12.8mmol). The reaction mixture is allowed to warm to 23°C and TMSOTf (100ml) is added and the solution is stirred for 24h. The mixture is poured into a saturated $NaHCO_3$ solution (50ml) and the organic phase is diluted with CH_2Cl_2 (50 ml). The aqueous phase is extracted with CH_2Cl_2 (2x25ml) and the combined organic phases are dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography (CH_2Cl_2/MeOH, 9:1) giving tetra-benzyl C-allylmannose **3(14)** as a single α-anomer.

(c) To a solution of **3(14)** (679mg, 1.20mmol) in CH_2Cl_2:MeOH (8ml:4ml) at -78°C is bubbled O_3 in O_2 until a blue color persists. To remove residual O_3, pure O_2 is bubbled through until the solution turns clear. DMS (1.7ml, 24.0 mmol) is added and the reaction mixture is warmed to 23°C and stirred for 24h. The reaction mixture is evaporated and partitioned bet-

ween a saturated $NaHCO_3$ solution (50ml) and EtOAc (5ml). The aqueous phase is extracted with EtOAc (2x30ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography (CH_2Cl_2/MeOH) giving perbenzyl aldehyde **4(14)**.

(d) 2 mol (1132mg) of **4(14)** is dissolved in a mixture of THF and water (3:1) and hydrogenated at 1 atm in the presence of a catalytic amount of Pd/C (Aldrich; 10% Pd/C). The mixture is allowed to react overnight and the catalyst is filtered off using a celite pad. The solvent is evaporated under vacuum and **5(14)** is isolated as a mixture of aldehyde and dihydrate.

Example A13: Preparation of D-glucose C-glycoside aldehyde 12 (14)

Starting with methyl α-D-glucopyranoside (1.96g, 9.61 mmol) compound **12(14)** is prepared in analogy with Example A12.

Example A14: Preparation of compound 21(14)

(a) 5 mmol of **2(14)** is dissolved in dry acetonitrile (5 ml, 1.0) and 2 equivalents of allyl trimethyl silane are added followed by 0.5 eq of TMSOTf under argon. The mixture is allowed to react for 48h and acetic anhydride (2 eq) is added. After 10 min, the reaction is subjected to extractive work-up (ether/water) and purified by chromatography to yield 3.25 mmol (65%) of acetylated product. Deprotection is carried out by treatment with NaOMe in MeOH for 30 min and filtration through Dowex-H^+ affords 3-(α-2,3,4-O-tribenzylmannopyranosyl)-1-propene **15(14)**.

(b) **15(14)** is subjected to a standard Mitsunobu reaction [Mitsunobu et al. Synthesis 1 (1981)] using PPh_3 and diethyl azodicarboxylate with diphenyl phosphoryl azide as nucleophile. Purification by flash chromatography yields 3-(α-6-azide-2,3,4,tri-O-benzylmannopyranosyl)-1-propenal **19(14)**.

(c) **19(14)** is treated with 1.5 eq of PPh_3 in THF as solvent and in the presence of 1.5 eq of water for 3 h at RT. Purification is carried out by flash chromatography and the resulting amine is coupled with succinic anhydride (1.1 eq) and triethyl amine (1.1 eq) in MeOH [Uchiyama et al. Bioorg. & Med. Chem., 4: 1149 (1996)] to yield **20(14)**.

(d) **20(14)** is exposed to EDT/HOBt mediated coupling (conditions vida supra) of the acid selected from the group consisting of acetic acid, phenylacetic acid and decanoic acid which is then subjected to ozonolysis in DCM/MeOH (5:1), quenched by DMS and extracted

from ether. Hydrogenation of the benzyl groups is carried out in THF:H_2O mixture under 50 psi of H_2 to yield **21(14)**.

Example A15: Preparation of Compound 22(14)

20(14) is treated with 1.1 eq of succinic anhydride in pyridine as solvent and in the presence of a catalytic amount of DMAP; conditions and workup are as above. The product so obtained is subjected to ozonolysis in DCM/MeOH (5:1), quenched by DMS and extracted from ether. Hydrogenation of the benzyl groups is carried out in THF:H_2O mixture under 50 psi of H_2 to yield **22(14)**.

Example A16: Preparation of 3-(α-6-sulphate-mannopyranosyl)-1-propenal 17(14)

Treatment of **15(14)** with 1.2 eq of sulfur trioxide pyridine complex in DMF as solvent according to Turvey et al. [Adv. Carb. Chem. Biochem. 20:183 (1965)]. The sulfated sugar is then subjected to ozonolysis in MeOH and quenched with DMS. Hydrogenation of the benzyl groups is carried out in THF:H_2O mixture under 50 psi of H_2 using standard conditions and workup as described supra to yield **17(14)**.

Example A17: Preparation of diacid derivative 18(14)

15(14) is treated with 1.1 eq of succinic anhydride in pyridine as solvent and in the presence of a catalytic amount of DMAP. The product so obtained is coupled with dibenzylglutamic acid using EDC/HOBt coupling system (conditions vida supra). Extractive workup (ether/water) gives the protected precursor, that is subjected to ozonolysis in DCM/MeOH (5:1) quenched by DMS and extracted from ether (conditions vida supra). Hydrogenation of the benzyl groups is carried out in THF:H_2O mixture under 50 psi of H_2 to yield **18(14)** using standard conditions and workup as described supra.

Example A18: Preparation of L-fucose C-glycoside template

Starting from methyl α-L-fucopyranoside the L-fucose C-glycoside template is prepared according to Example A12.

Example A 19: Preparation of D-mannose O-glycoside 26(14)

(a) The O-allyl, O-propenyl, O-butenyl, and O-pentenyl α-(D)-glucoside **23(14)** is prepared according to Fraser-Reid et al [Syntlett 927 (1992)] wherein the O-methyl α-(D)-mannoside

is stirred in neat solvent (e.g. 1.0 propenol (for the O-propenyl derivative), 1.0 allyl alcohol (for the O-allyl derivative), 1.0 butenol (for the O-butenyl derivative) or 1.0 O-pentenol (for the O-pentenyl derivative) at 90°C for 12 h. The product is then worked up and purified employing standard conditions vida supra.

(b) 700mg (2.8 mmol) of the O-allyl, O-propenyl, O-butenyl, or O-pentenyl α-(D)-mannoside **23(14)** and 420 mg (6.2 mmol) of imidazole are dissolved in 3 ml anhydrous DMF and cooled down to 0°C. The solution is treated dropwise (15 min) with 810 µl (3.1 mmol) of TBDPSCl and the ice bath is removed. After stirring at RT for 2 h the reaction is quenched by addition of EtOAc and brine. The aqueous layer is extracted (2x) with EtOAc and the combined organic layers are dried over Na_2SO_4, and concentrated. The crude mixture is chromatographed (70 g silica gel, Hex/EtOAc 1:1) to afford a slightly yellow oil.

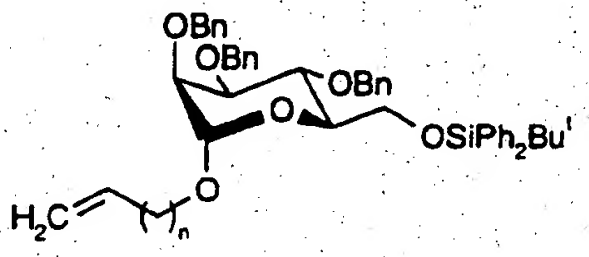
950mg (1.94 mmol) of the triol are dissolved in 4ml of anhydrous THF and 36 mg (0.097 mmol) of TBAI and 1.15 ml (9.7 mmol) of BnBr are added. To the ice cooled solution 330mg (95%, 7.8 mmol) of NaH are added at once and the mixture is stirred overnight and allowed to warm up to RT. Under ice cooling the heterogeneous mixture is quenched with sat. NH_4Cl and after diluting with brine the mixture is extracted with ethyl ether (2x, 100ml). The combined organic layers are dried with $MgSO_4$ and concentrated in vacuo. The crude mixture is chromatographed (100 g silica gel, Hex/Et_2O 10:1) to give a slightly yellow oil.

(c) To a solution of the above prepared terminal olefin (679 mg, 1.20 mmol) in CH_2Cl_2:-MeOH (8 ml:4ml) at -78°C is bubbled O_3 in O_2 until a blue color persists. To remove residual O_3, pure O_2 is bubbled through until the solution turns clear. DMS (1.7 ml, 24.0 mmol) is added and the reaction mixture is warmed to 23°C and stirred for 24 h. The reaction mixture is evaporated and partitioned between a saturated $NaHCO_3$ solution (50 ml) and EtOAc (5 ml). The aqueous phase is extracted with EtOAc (2x30ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography (CH_2Cl_2:MeOH) giving the perbenzyl aldehyde. The tert-butyldiphenylsilyl moiety is then removed by adding 1.0 M solvent THF to the perbenzyl aldehyde followed by the addition of TBAF (1.0 equivalents; 1.0 M solution). The reaction mixture is stirred for 2 h at 0°C. The reaction mixture is evaporated and partitioned between a saturated $NaHCO_3$ solution (50ml) and EtOAc (5ml). The aqueous phase is extracted with EtOAc (2x30ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography (CH_2Cl_2:MeOH) giving the perbenzylated aldehyde 25(14).

(d) 2 mmol (1132 mg) of compound **25(14)** is dissolved in a mixture of THF and water (3:1) and hydrogenated at 1 atm in the presence of a catalytic amount of Pd/C. The mixture is allowed to react overnight and the catalyst is filtered off using a celite pad. The solvent is evaporated under vacuum and the product **26(14)** is obtained.

Example A20: Preparation of compound 28(14)

(a) The tertbutyldiphenylsilyl moiety of **24(14)**



is removed by adding 1.0 solvent THF to the perbenzyl aldehyde followed by the addition of TBAF (1.0 equivalents; 1.0 M solution). The reaction mixture is stirred for 2 h at 0°C. The reaction mixture is evaporated and partitioned between a saturated $NaHCO_3$ solution (50ml) and EtOAc (5 ml). The aqueous phase is extracted with EtOAc (2x 30ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography (CH_2Cl_2 / MeOH) to provide the free alcohol. The free alcohol is dissolved in 4 ml of anhydrous methylene chloride and 1.1 equivalents of R'-bromide (chloride or iodide is also acceptable) is added wherein R' is selected from the group consisting of OH, H, N_3, OSO_3^{2-}, $OCOCH_2CH_2CONHCH(CH_2CO_2H)CO_2H$, NHR' (R' = alkyl, acyl, decanoyl, phenylacetyl, $COCH_2CH_2H$) followed by 1.1 equivalents of NaH and the mixture is stirred overnight and allowed to warm up to RT. Under ice cooling the heterogeneous mixture is quenched with sat. NH_4Cl and after diluting with brine the mixture is extracted with ethyl ether (2x, 100ml). The combined organic layers are dried with $MgSO_4$ and concentrated in vacuo. The crude mixture is chromatographed by silica gel flash chromatography (CH_2Cl_2 / MeOH) to provide the protected olefin **27(14)**.

(b) To a solution of **27(14)** (679 mg, 1.20 mmol) in CH_2Cl_2:MeOH (8ml:4ml) at -78°C is bubbled O_3 in O_2 until a blue color persists. To remove residual O_3, pure O_2 is bubbled through until the solution turns clear. DMS (1.7 ml, 24.0 mmol) is added and the reaction mixture is warmed to 23°C and stirred for 24 h. The reaction mixture is evaporated and partitioned between a saturated $NaHCO_3$ solution (50ml) and EtOAc (5ml). The aqueous phase is extracted with EtOAc (2x30ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography

(CH_2Cl_2/MeOH) giving the perbenzyl aldehyde. 2 mmol (1132mg) of the perbenzyl aldehyde is dissolved in a mixture of THF and water (3:1) and hydrogenated at 1 atm in the presence of a catalytic amount of Pd/C. The mixture is allowed to react overnight and the catalyst is filtered off using a celite pad. The solvent is evaporated under vacuum to afford **28(14)**.

Example A21: Preparation of D-glucose O-glycoside template

The synthesis of the D-glucose O-glycoside template is achieved in exactly the same steps as that of D-mannose outlined in Example A19 or A20.

Example A22: Preparation of L-fucose O-glycoside template

10 mmol of L-fucose are placed in a roundbottom flask together with a large excess of allyl alcohol and heated to 90°C. Then 1eq of boron trifluoride etherate is added dropwise and the mixture is allowed to react overnight. Next, the bulk of allyl alcohol is removed by evaporation in vacuo and the residue is passed through a silica gel column using ethyl acetate:-hexane as eluent, first 1:4 to elute the remaining allyl alcohol and then 1:1 to elute the fucose glycoside off the column mainly as α anomer.

To a solution of the above prepared terminal olefin (679mg, 1.20 mmol) in CH_2Cl_2:MeOH (8ml:4ml) at -78°C is bubbled O_3 in O_2 until a blue color persists. To remove residual O_3, pure O_2 is bubbled through until the solution turns clear. DMS (1.7ml,24.0mmol) is added and the reaction mixture is warmed to 23°C and stirred for 24h. The reaction mixture is evaporated and partitioned between a saturated $NaHCO_3$ solution (50ml) and EtOAc (5 ml). The aqueous phase is extracted with EtOAc (2 x 30ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography (CH_2Cl_2 / MeOH) giving the L-fucose O-glycoside template.

Example A23: Preparation of compound 18(15)

(a) Synthesis of Compound **14(15)**: To a solution of methyl β-D-galactopyranoside (10 g, 51.5 mmol) in CH_3CN (250 ml) is added benzaldehyde dimethyl acetal (15.6 ml, 103 mmol) followed by CSA (1.19 g, 5.15 mmol). After 30 min ET_3N (1 ml) is added and the solvent is removed under reduced pressure and the crude solid is recrystallized from hot MeOH affording **14(15)**.

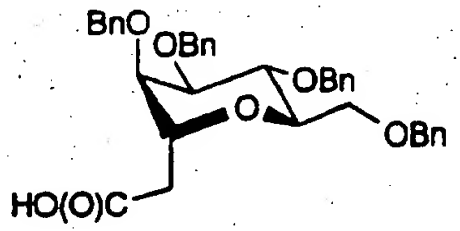
(b) Synthesis of Compound 3-allyl-4,6-benzylidene-2-hydroxy β-D-methylgalactopyranoside **15(15)**: To a solution of **14(15)** (4.7 g, 16.7 mmol) in toluene (55 ml) is added BU_2SnO (4.56

g, 18.3 mmol) and the solution is dehydrated using a Dean-Stark trap (130°C, 2 h). The reaction mixture is cooled to 70°C and TBAI (4.3 g, 11.7 mmol) is added followed by allylbromide (2.18 ml, 25 mmol). The solution is stirred at 130°C for 24 h before being cooled to 23°C and partitioned between EtOAc (200 ml) and saturated $NaHCO_3$ (200 ml). The aqueous layer is extracted with EtOAc (2 x vol) and the combined organic layers are dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (1:1 to 100% EtOAc/Hexane) giving **15(15)**.

(c) Synthesis of Compound **16(15)**: To a solution of $(COCl)_2$ (209 ml, 2.40 mmol) in CH_2Cl_2 (4 ml) at -78°C is added DMSO (341 ml, 78.1 mmol). The reaction mixture is warmed to 0°C for 5 min and the re-cooled to -78°C. **15(15)** (704 mg, 2.19 mmol) is dissolved in CH_2Cl_2 (4 ml) and added slowly drop-wise. The reaction mixture is stirred for 30 min and DIPEA is added (1.48ml, 10.9 mmol). The reaction mixture is warmed to 23°C, diluted with CH_2Cl_2 (100 ml), washed with saturated $NaHCO_3$ (50 ml), and dried ($MgSO_4$). The crude product is used directly in the next step without further purification.

To a solution of the above ketone in MeOH (20 ml) is added NH_4OAc until the solution is saturated. Sodium cyanoborohydride (116 mg, 2.19 mmol) is added and the reaction mixture is stirred for 48 h. The reaction mixture is partitioned between EtOAc (100 ml) and saturated $NaHCO_3$ (50 ml) and the aqueous layer is further extracted with EtOAc (2 x 50 ml). The combined organic layers are dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (5% MeOH/ CH_2Cl_2) giving **16(15)**.

(d) Synthesis of Compound **17(15)**: To a solution of **8(15)**



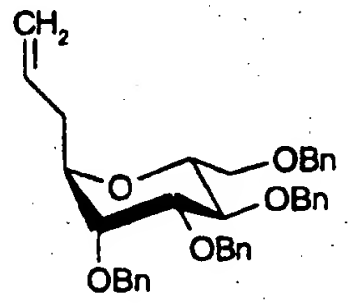
(806 mg, 1.38 mmol) in methylene chloride (5 ml) at 0°C is added DIPEA (510 ml, 2.86 mmol) followed by $(COCl)_2$ (120 ml, 1.38 ml). The solution is stirred for 15 min at 0°C before **16(15)** (296 mg, 0.92 mmol) is added as a solution in methylene chloride (1 ml). The reaction mixture is gradually warmed to 23°C and stirred for 24 h. The reaction mixture is diluted with CH_2Cl_2 (50 ml) washed with a $NaHCO_3$ solution (25 ml), dried ($MgSO_4$), and the solvent is removed under reduced pressure. The crude oil is purified by SGCC (5% MeOH:CH_2Cl_2) giving **17(15)**.

(e) Synthesis of Compound **18(15)**: To a solution of **17(15)** (300 mg, 339 mmol) in methylene chloride:MeOH (3 ml:1 ml) at -78°C is bubbled O_3 in O_2 until a blue color persists. To remove residual O_3, pure O_2 is bubbled through until the solution turns clear. PPh_3 (98 mg, 372 mmol) is added and the reaction mixture is warmed to 23°C and stirred for 24 h. The reaction mixture is evaporated and partitioned between a saturated $NaHCO_3$ solution (50 ml) and CH_2Cl_2 (5 ml). The aqueous phase is extracted with CH_2Cl_2 (2 x 30 ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is used directly without further purification.

The aldehyde prepared above is dissolved in acetone (3 ml) and cooled to 0°C. Jones reagent is added drop-wise until a orange color persists. iPrOH (1 ml) is added to quench any excess Jones reagent and the reaction mixture is then partitioned between methylene chloride (50 ml) and 1 N HCl (50 ml). The aqueous layer is extracted with CH_2Cl_2 (50 ml) and the combined organic phases are dried ($MgSO_4$), concentrated under reduced pressure, and purified by silica gel flash chromatography (100% EtOAc) giving **18(15)**.

Example A24: Preparation of compound 23(15)

(a) Synthesis of Compound **20(15)**: To a solution of the terminal olefin



(500 mg, 0.887 mmol; intermediate from **7(15)**) in benzene (50 ml) is added $PdCl_2$ (catalytic) and the solution is heated to reflux for 24 h. The reaction mixture is filtered through Celite, evaporated, and the crude oil is purified by silica gel chromatography (EtOAc:Hexane 1:9 to 1:1) giving **20(15)**.

(b) Synthesis of compound **21(15)**: Starting from a solution of **20(15)** (230 mg, 0.407 mmol) in methylene chloride (20 ml) **21(15)** is prepared according to Example A30(d).

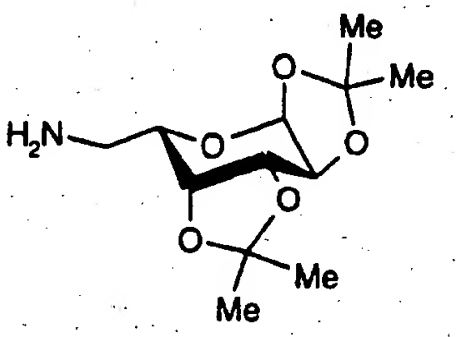
(c) Synthesis of compound **22(15)**: To a solution of **16(15)** (65 mg, 0.203 mmol), **21(15)** (150mg, 0.264 mmol), NMM (45 ml, 0.407), and HOBt (41.1 mg, 0.305 mmol) in CH_2C_{12} (3 ml) at 0°C is added EDC (60.1 mg, 0.305 mmol). The reaction mixture is warmed to 23°C and stirred for 24h. The reaction mixture is diluted with EtOAc (50 ml) and washed successively with a 5% citric acid solution (20 ml) and saturated $NaHCO_3$ (20 ml). The solvent is re-

moved under reduced pressure, dried ($MgSO_4$), and the crude oil is purified by silica gel chromatography (EtOAc:Hexane 1:3 to 3:1) giving **22(15)**.

(d) Synthesis of Compound **23(15)**: Starting from a solution of **22(15)** (100 mg, 0.114 mmol) in methylene chloride (10 ml) **23(15)** is prepared according to Example A30(d) wherein the last purification step is silica gel flash chromatography (EtOAc:HOAc 95:5).

Example A 25: Preparation of compound 26(15)

To a solution of **25(15)**



25(15)

(100 mg, 0.386 mmol) obtained following Cappi et al. [Angew. Chem. 108:2501 (1996)] in MeOH (2 ml) at 23°C is added succinic anhydride (38 mg, 0.386 mmol) and the reaction mixture is stirred for 24 h at 23°C. The reaction mixture is concentrated under reduced pressure and the crude oil is purified by silica gel chromatography giving **26(15)**.

Example A 26: Preparation of Compound 28(15)

Starting from **25(15)** and glutaric anhydride (44 mg, 0.386 mmol) **28(15)** is prepared in analogy to Example A25.

Example A29: Preparation of methyl 3-allyloxy-2-amino-4,6-benzylidene-β-D-galactopyranoside 12(3)

To a solution of methyl β-D-galactopyranoside (10 g, 51.5 mmol) in CH_3CN (250 ml) is added benzaldehyde dimethyl acetal (15.6 ml, 103 mmol) followed by CSA (1.19 g, 5.15 mmol). After 30 min Et_3N (1 ml) is added and the solvent is removed under reduced pressure and the crude solid is recrystallized from hot MeOH affording the benzylidene acetal.

To a solution of the above galactose benzylidene acetal (4.7g, 16.7 mmol) in toluene (55 ml) is added Bu_2SnO (4.56 g, 18.3mmol) and the solution is dehydrated using a Dean-Stark trap (130°C, 2 h). The reaction mixture is cooled to 70°C and TBAI (4.3 g, 11.7 mmol) is

added followed by allylbromide (2.18 ml, 25 mmol). The solution is stirred at 130°C for 24 h before being cooled to 23°C and partitioned between EtOAc (200 ml) and saturated $NaHCO_3$ (200 ml). The aqueous layer is extracted with EtOAc (2 x vol) and the combined organic layers are dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (1:1 to 100% EtOAc/Hexane) giving the product intermediate.

To a solution of $(COCl)_2$ (209 µl, 2.40 mmol) in CH_2Cl_2 (4 ml) at -78 C is added DMSO (341 µl, 78.1 mmol). The reaction mixture is warmed to 0°C for 5 min and then re-cooled to -78°C. 3-Allyl-4,6-benzylidene-2-hydroxy β-D-methylgalactopyranoside (704 mg, 2.19 mmol) is dissolved in CH_2Cl_2 (4 ml) and added slowly drop-wise. The reaction mixture is stirred for 30 min and DIPEA is added (1.48 ml, 10.9 mmol). The reaction mixture is warmed to 23°C, diluted with CH_2Cl_2 (100 ml), washed with saturated $NaHCO_3$ (50 ml), and dried ($MgSO_4$). The crude product is used directly in the next step without further purification.

To a solution of the above ketone in MeOH (20 ml) is added NH_4OAc until the solution is saturated. Sodium cyanoborohydride (116 mg, 2.19 mmol) is added and the reaction mixture is stirred for 48 h. The reaction mixture is partitioned between EtOAc (100 ml) and saturated $NaHCO_3$ (50 ml) and the aqueous layer is further extracted with EtOAc (2 x 50 ml). The combined organic layers are dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (5% MeOH/ CH_2Cl_2) giving **12(3)**.

Example A30: Preparation of methyl-2-[N-(2,3,4,6-tetrabenzyloxy-α-D-mannopyranoside)carbonyl]amino-3-[(2-acetic acid)oxy]-4,6-O-dibenzylidine-galactopyranoside 13(3)

(a) Synthesis of -O-acetyl-1-allyl-2,3,4-tri-O-benzyl-α-D-mannopyranoside **8(3)**: To a solution of methyl 2,3,4,6-tetra-O-benzyl-α-mannoside (0.69 mmol) in CH_3CN (1.4 ml) is added allyltrimethylsilane (1.45 mmol) at 0°C under argon. To the mixture is added TMSOTf (0.35 mmol) and the reaction is kept stirring under the same temperature overnight, then warmed up to 25°C. To the mixture is added acetic anhydride (1 ml) drop by drop. After 5 min, the reaction is diluted with CH_2Cl_2 (10 ml) and the resulting solution is quenched by saturated NaHCO. The aqueous layer is extracted with CH_2Cl_2 (2 x 10 ml) and the combined organic layers are washed with brine, dried with $MgSO_4$, filtered, evaporated and purified by column chromatography to provide **8(3)**.

(b) Synthesis of Compound **9a(3)**: To a solution of **8(3)** (1.00 g, 2.11 mmol) is added 0.3 equivalents of sodium methoxide in 1.0 M methanol and is stirred at 25°C for 6 h; the

solution is concentrated and to the crude is added 95% NaH (0.10 g, 2.74 mmol) at 0°C under argon. After 30 min, to the mixture is added BnBr (0.84 ml, 2.74 mmol) followed by TBAI (37.4 mg, 0.11 mmol) and the resulting solution is warmed up to 25°C overnight. The reaction is quenched by H_2O (10 ml), then extracted with EtOAc (3 x 10 ml) and the combined organic layers are washed with brine, dried with $MgSO_4$, filtered, evaporated and purified by column chromatography (hexane to EtOAc/hexane = 1/20) to yield **9a(3)**.

(c) Synthesis of 1-(1-propenyl)-2,3,4,6-tetra-O-benzyloxy-α-D-mannopyranoside **10(3)**: To a solution of **9a(3)** (500 mg, 0.887 mmol) in benzene (50 ml) is added $PdCl_2$ (catalytic) and the solution is heated to reflux for 24 h. The reaction mixture is filtered through Celite, evaporated, and the crude oil is purified by silica gel chromatography (EtOAc:Hexane 1:9 to 1:1) giving **10(3)**.

(d) Synthesis of 1-(2,3,4,6-tetra-O-benzyloxy-α-D-mannopyranosyl)-formic acid **11(3)**: To a solution of **10(3)** (230 mg, 0.407 mmol) in CH_2Cl_2 (20 ml) at -78°C is bubbled O_3 until a blue color persists. To remove residual O_3, pure O_2 is bubbled through until the solution turns clear. DMS (1.0 ml) is added and the reaction mixture is warmed to 23°C and stirred for 24 h. The reaction mixture is concentrated under reduced pressure. The crude oil is used directly without further purification.

The aldehyde prepared above is dissolved in acetone (5 ml) and cooled to 0°C. Jones reagent is added drop-wise until an orange color persists. ^{i}PrOH (1 ml) is added to quench any excess Jones reagent and the reaction mixture is then partitioned between EtOAc (50 ml) and 1 N HCl (50 ml). The aqueous layer is extracted with EtOAc (50 ml) and the combined organic phases are dried ($MgSO_4$), concentrated under reduced pressure, and purified by silica gel flash chromatography (EtOAc:Hexane:HOAc 3:1:0.01) giving **11(3)**.

(e) Synthesis of **13(3)**: To a solution of **12(3)** (65 mg, 0.203 mmol), **11(3)** (150 mg, 0.264 mmol), NMM (45 µl, 0.407), and HOBt (41.1 mg, 0.305 mmol) in CH_2Cl_2 (3 ml) at 0°C is added EDC (60.1 mg, 0.305 mmol). The reaction mixture is warmed to 23°C and stirred for 24 h. The reaction mixture is diluted with EtOAc (50 ml) and washed successively with a 5% citric acid solution (20 ml) and saturated $NaHCO_3$ (20 ml). The solvent is removed under reduced pressure, dried ($MgSO_4$), and the crude oil is purified by silica gel chromatography (EtOAc:Hexane 1:3 to 3:1) giving **13(3)**.

Example A31: Preparation of dibenzyl N-[1-(6-O-hexadecanyl-2,3,4-tri-O-*benzyl*-α-D-mannopyranosyl)]-acetyl-L-glutamate 17(3)

(a) Synthesis of 1-allyl-6-O-hexadecanyl-2,3,4-tri-O-benzyl-α-D-mannopyranoside **9b(3)**: To a solution of acetate **8(3)** (1.00 g, 2.11 mmol) is added 0.3 equivalents of sodium methoxide in 1.0 M methanol and is stirred at 25°C for 6 h; the solution is concentrated and to the crude is added 95% NaH (0.10 g, 2.74 mmol) at 0°C under argon. After 30 min, to the mixture is added 1-bromohexadecane (0.84 ml, 2.74 mmol) followed by TBAI (37.4 mg, 0.11 mmol) and the resulting solution is warmed up to 25°C overnight. The reaction is quenched by H_2O (10 ml), then extracted with EtOAc (3 x 10ml) and the combined organic layers are washed with brine, dried with $MgSO_4$, filtered, evaporated and purified by column chromatography (hexane to EtOAc/hexane = 1/20) to yield **9b(3)**.

(b) Synthesis of **17(3)**: Step (a): Starting from a solution of **9b(3)** (679 mg, 1.20 mmol) in CH_2Cl_2:MeOH (8 ml:4 ml) the corresponding carboxylic acid intermediate is prepared according to Example A30(d).

Step (b): To a solution of carboxylic acid intermediate (50 mg, 0.086 mmol), H-Glu-$(OBn)_2$ • pTsOH (0.095 mmol), HOBt (12.8 mg, 0.095 mmol), and NMM (10.3 µl, 0.095 mmol) in CH_2Cl_2, (500 µl) at 0°C is added EDC (18 mg, 0.095 mmol). The reaction is allowed to stir for 24 h before being diluted with CH_2Cl_2 (50 ml) and washed successively with a citric acid solution (25 ml), saturated $NaHCO_3$ solution (25 ml), and brine (25ml). The organic phase is dried ($MgSO_4$), concentrated under reduced pressure, and purified by silica gel chromatography (EtOAc:Hexane 1:1) giving **17(3)**.

(Alternatively, the following alkyl halide or acyl halide may be used in lieu of 1-bromohexadecane: 1-chloropropane, 1-chlorobutane, 1-chloropentane, 1-chlorohexane, 1-chloroheptane, 1-chlorooctane, 1-chlorononane, 1-chlorodecane, 1-bromoundecane, 1-bromododecane, 1-bromotridecane, 1-bromotetradecane, 1-bromopentadecane, 1-bromohexadecane, 1-bromooctadecane, 1-bromoeicosane, 1-bromodocosane, 2-bromomethyl-naphthalene, 1-chloromethyl-naphthalene, 2-bromoethyl-benzene, 1-bromo-3-phenyl-propane, heptanoyl chloride, octanoyl chloride, nonaoyl chloride, decanoyl chloride, undecanoyl chloride, lauroyl chloride, myristoyl chloride, palmitoyl chloride, heptadecanoyl chloride and stearoyl chloride)].

Example A32: Preparation of 18(3)

D-Mannose (1500 mg, 8.3 mmol) is added to 10 ml of allyl alcohol together with a catalytic amount (10 mg) of camphorsulfonic acid. The mixture is heated to 90°C overnight and then

the excess allyl alcohol is evaporated in vacuo. Flash chromatography of the residue (EtOAc:MeOH, 6:1 -4:1) gives 1400 mg (76%) of α-O-allylmannopyranoside.

To a solution of the above compound is added 1.1 equivalents TBDPSOTf (1.1 equivalents) in anhydrous methylene chloride (.10 M) at 0°C and allowed to stir for 2 h. Next, 3.3 equivalents of sodium hydride are added, followed by 3.3 equivalents BnBr. The mixture is allowed to stir overnight at 0°C and extracted with CH_2Cl_2 and washed with 1 N HCl, saturated $NaHCO_3$, and brine, and purified by flash chromatography using EtOAc as eluent.

Next, 1.1 equivalents of TBAF are added in anhydrous methylene chloride (.10 M) at 0°C and allowed to stir for 2 h. The mixture is then extracted with CH_2Cl_2 and washed with ammonium chloride, saturated $NaHCO_3$, and brine, and purified by flash chromatography using EtOAc as eluent.

Next, 1.1 equivalents of sodium hydride are added in anhydrous methylene chloride mixture (.10 M) at 0°C and then 1.1 equivalents of either an alkyl halide or acyl halide as mentioned in Example A31(a) are added and allowed to stir for 2 h. The mixture is then extracted with CH_2Cl_2 and washed with ammonium chloride, saturated $NaHCO_3$, and brine, and purified by flash chromatography using EtOAc as eluent.

To a solution of the above compound (482 mg, 2.2 mmol) in CH_2Cl_2:MeOH (1:4) is bubbled O_3 at -78°C in the presence of a catalytic amount of $NaHCO_3$. After the blue color appears, an excess (3 eq) of PPh_3 is added. After stirring overnight, an extractive workup is performed (CH_2Cl_2/water), the aqueous portion is evaporated affording **18(3)**.

Example A33: Preparation of 18a(3)

The ozonolysis of **9a(3)** is performed as described above. The aldehyde product (2 mmol, 1.1 g) is dissolved in a 3:1 mixture of THF and water and hydrogenated overnight at 1 atm in the presence of a catalytic amount of Pd-C. After filtration through Celite and evaporation of the solvent, the deprotected aldehyde **18a(3)** is isolated.

Example A34: Preparation of compound 63(3)

(a) Synthesis of allyl 6-tosyl-6-deoxy-D-mannopyranoside **60(3)**: To a solution of allyl mannopyranoside (6.6 g, 30 mmol; formed by refluxing neat allyl alcohol with mannose in the presence of .01 equivalents CSA or equivalent) in dry pyridine (75 ml) at 0°C is added tosyl chloride (10.3 g, 54 mmol) dissolved in CH_2Cl_2, and the reaction is stirred at 0°C for 16 h and at RT for 4h. The reaction mixture is extracted with CH_2Cl_2 and washed with 1 N HCl,

saturated $NaHCO_3$, and brine, and purified by flash chromatography using EtOAc as eluent to yield **60(3)**.

(b) Synthesis of allyl 6-azido-6-deoxy-D-mannopyranoside **61(3)**: To a solution of **60(3)** (1.6 g, 9.3 mmol) in DMF (50 ml) is added 10 equiv (4.1 g) of NaN_3, and this mixture is refluxed overnight, the solvent removed in vacuo, and the residue chromatographed in SiO_2 using EtOAc as eluent to yield **61(3)**.

(c) Synthesis of Compound **62(3)**: A solution of **61(3)** (482 mg, 2.2 mmol) and catalytic amount of $NaHCO_3$ (10 mg) in CH_2Cl_2/MeOH (4/1, 40 ml) is cooled to -78°C. O_3 is bubbled through the solution until a blue color is observed (10 min) then N_2 is bubbled through the solution until it becomes colorless. Dimethyl sulfite (577 mg, 6.6 mmol) is added and the mixture is warmed to RT and stirred overnight. After filtrated, the solvent is evaporated under reduced pressure. The residue is dissolved in water and washed with ether. The water layer is lyophilized to yield **62(3)**.

(d) Synthesis of Compound **63(3)**: **62(3)** (330 mg, 1.5 mmol) and DHAP (0.5 mmol) are dissolved in Tris buffer (50 mM, pH 7.4) 10 ml. The pH is adjusted to 7.0 by adding 1 N NaOH and then 200 u of RAMA (Sigma) is added. The reaction mixture is shaken under nitrogen at RT. The progress of the reaction is followed by DHAP consumption (UV assay) until >90% of the DHAP has been consumed. The pH is adjusted to 7.5 and $BaCl_2$-H_2O (1.0 M, 2 mmol) is added slowly. The cloudy mixture is kept at 4°C for 1 h and the precipitates are removed by centrifugation. To the supernatant 2 volumes of acetone are added and the mixture is stored at 9°C for 2 h. The precipitates are collected by centrifugation and the supernatant is discarded. The pellet is treated with Dowex-50 H^+ to pH 2 (the solid is dissolved) and the resin is filtered off. The pH of the filtrate is adjusted to 7.0-7.5 by adding 0.2 N NaOH. Lyophilization yields **63(3)**.

Example A35: Preparation of 68(3)

(a) Synthesis of 6-O-acetyl-1-allyl-2,3,4-tri-O-benzyl-α-D-mannopyranoside **65(3)**: To a solution of methyl 2,3,4,6-tetra-O-benzyl-α-mannoside (0.69 mmol) in CH_3CN (1.9 ml) is added allyltrimethylsilane (1.45 mmol) at 0°C under argon. To the mixture is added TMSOTf (0.35 mmol) and the reaction is kept stirring under the same temperature overnight, then warmed up to 25°C. To the mixture is added acetic anhydride (1 ml) drop by drop. After 5 min, the reaction is diluted with CH_2Cl_2 (10 ml) and the resulting solution is quenched by saturated $NaHCO_3$. The aqueous layer is extracted with CH_2Cl_2 (2 x 10 ml) and the combined organic

layers are washed with brine, dried with $MgSO_4$, filtered, evaporated and purified by column chromatography to provide the acetate.

The crude acetate is dissolved in MeOH and a catalytic amount of 25% NaOMe by weight is added in MeOH. After 2 h Dowex H^+ resin is added until the pH of the solution is approximately 1-2. The residue is then dissolved in CH_2Cl_2 and the solution is washed with 5% aq. citric acid solution , sat. $NaHCO_3$ soln., and brine. This solution is then dried over Na_2SO_4 and concentrated under reduced pressure. The crude material is purified by flash chromatography with silica gel using 25%-35% ethyl acetate in hexane as the eluent.

The product is dissolved in methylene chloride (1.0 M) and exposed to PPh_3 (1.1 equivalents) and DEAD (1 equivalent) and finally $(PhO)_2PON_3$ (1.1 equivalents) is added dropwise at 0°C and the mixture is stirred for 1-2 h. The residue is dissolved in CH_2Cl_2 and the solution is washed with 5% aq. citric acid solution, sat. $NaHCO_3$ soln., and brine. This solution is then dried over Na_2SO, and concentrated under reduced pressure. The crude material is purified by flash chromatography with silica gel using 25%-35% ethyl acetate in hexane as the eluent to provide **65(3)**.

(b) Synthesis of N-(di-O-benzylglutamyl)-2-[(6-azido-2,3,4-tri-O-benzyloxy)-α-D-manno-pyranosyl)]-ethamide **67(3)**: To a stirred solution of **65(3)** (2.05 g, 4.1 mmol) and NMO (480 mg, 4.1 mmol) in 36 ml of a 9:2:1 mixture of acetone: tert-butanol:H_2O, is added OsO_4 (380 µl, 0.004 mmol) as a 2.5 wt% solution in tert-butanol. After stirring overnight, the reaction is quenched by the addition of 1 g Na_2S_2Os, 10 g Florisil and 25 ml of H_2O. After 30 min, the reaction mixture is concentrated under reduced pressure and the residue is treated with EtOAc and water. The solution is decanted away from the Florisil and the aqueous portion is extracted four times with EtOAc. The combined organic extracts are dried over $MgSO_4$ and concentrated under reduced pressure. The diol is immediately used in the next reaction.

To a stirred solution of the diol in 55 ml of THF and 40 ml of H_2O, is added $NaIO_4$ (1.4 g, 6.5 mmol). After 15 min the reaction is quenched by the addition of H_2O and EtOAc. The aqueous portion is extracted three times with EtOAc. The combined organic extracts are dried over Na_2SO_4 and concentrated under reduced pressure. The aldehyde is then used immediately in the next reaction.

To a stirred 0°C solution of the aldehyde in 40 ml of acetone, is added Jones reagent until an orange color persists. Tlc analysis indicates the complete consumption of the starting material. The reaction is quenched with isopropanol, 5 g of celite is added and the reaction

is stirred for 20 min. The solution is decanted into a separatory funnel and EtOAc is added. The aqueous portion is extracted three times with EtOAc. The combined organic extracts are dried over $MgSO_4$ and concentrated under reduced pressure. The acid is sufficiently pure for use in the next reaction.

To a stirred, 0°C solution of the above carboxylic acid, amino acid (2.25 g, 4.5 mmol), HOBt (609 mg, 4.5 mmol) and NMM (496 µl, 4.5 mmol) in 60 ml of CH_2Cl_2, is added EDC (865 mg, 4.5 mmol). The reaction is allowed to slowly warm to RT overnight and the reaction is quenched by the addition of H_2O and CH_2Cl_2. The aqueous portion is extracted three times with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using 35% EtOAc in hexane to provide **67(3)**.

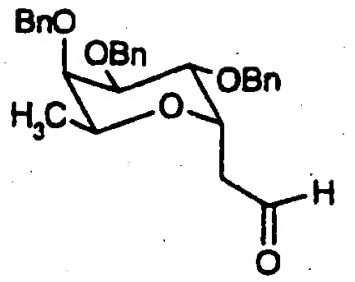
(c) Synthesis of Compound **68(3)**: To a stirred solution of **67(3)** (666 mg, 0.8 mmol) and PPh_3 (336 mg, 1.28 mmol) in 20 ml of THF, is added H_2O (23 µl, 1.28 mmol). After stirring overnight, hexanoic acid (0.96 mmol), HOBt (130 mg, 0.96 mmol) and NMM (106 µl, 0.96 mmol) are added. After cooling the mixture to 0°C, EDC (184 mg, 0.96 mmol) is added. The cold bath is removed after 10 min and the mixture is vigorously stirred to dissolve the remaining solid material. After stirring overnight, the reaction is quenched with 5% aqueous citric acid and Et_2O is added. The aqueous portion is extracted with Et_2O three times. The combined organic extracts are washed with sat. aqueous $NaHCO_3$ soln. and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to provide **68(3)**.

Example A36: Preparation of 71(3)

To a stirred solution of **68(3)** in 2 ml of HOAc are added 2 drops of H_2O, a catalytic amount of 10% Pd/C and H_2 gas. After stirring for 1 day, the catalyst is filtered off through a pad of celite and the pad is rinsed with HOAc. The filtrate is concentrated under reduced pressure to provide **71(3)**.

Example A37: Preparation of 78(3)

(a) Synthesis of N-(O-allylhexanoate)-2-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)ethylamine **73(3)**: $H_2N(CH_2)_5C(O)OCH_2CHCH_2$ (1 g, 5.8 mmol) is dissolved in 20 ml of MeOH and the pH of the solution is adjusted to pH 6 with glacial acetic acid. To this solution is added aldehyde



(533 mg, 1.3 mmol; aldehyde is synthesized via standard glycosylation conditions using 1-methoxy-tribenzyl-fucose and allytrimethylsilane (1.1 equivalents, THF (.5 Molar), TMSOTf (.1 equivalent) at 0°C for 5 h) followed by $NaCNBH_3$ (36 mg, 0.58 mmol). After 1 h the solution is concentrated under reduced pressure and the residue is treated with EtOAc and water. The pH of the solution is adjusted to pH 2 with 1 N HCl and the aqueous portion is extracted three times with EtOAc. The aqueous portion is then treated with solid KOH to adjust the pH to 10. The aqueous portion is again extracted three times with EtOAc and both organic portions are combined, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using 7% MeOH in CH_2Cl_2 to provide **73(3)**.

(b) Synthesis of (2*S*,3*S*)-2-tert-butoxycarbonylamino-3,4-dibenzyloxy-butanoic acid **74(3)**:

To a stirred 0°C solution of **73(3)** (992 mg, 2.3 mmol) in 20 ml of THF is added a 0°C solution of LiOH (23 ml, 5.7 mmol, 0.25 M in EtOH:H_2O (3:1)). The reaction is kept overnight at 4°C. Then the mixture is acidified to pH 2 with 1 N HCl and EtOAc is added. The aqueous portion is extracted with EtOAc three times. The combined organic extracts are dried over Na_2SO_4 and concentrated under reduced pressure to provide **74(3)**.

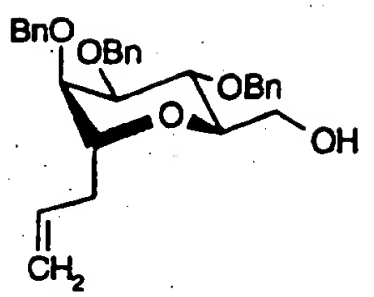
(c) Synthesis of N-(O-allylhexanoate)-1-{(2*S*,3*S*)-3,4-dibenzyloxy-2-tert-butoxycarbonyl-amino)-butyridiamidyl}-2-(2,3,4-tri-C-benzyl-α-L-fucopyranosyl)ethane **75(3)**: To a stirred 0°C solution of **73(3)** (31 mg, 0.05 mmol), **74(3)** (20.4 mg, 0.05 mmol), HOBt (7.9 mg, 0.05 mmol) and NMM (6.0 µl, 0.05 mmol) in 10 ml of CH_2Cl_2 is added HBTU (20.9 mg, 0.05 mmol). After warming to RT overnight, the reaction is quenched with 5% aqueous citric acid and CH_2Cl_2 is added. The aqueous portion is extracted with CH_2Cl_2 twice. The combined organic extracts are washed with sat. aqueous $NaHCO_3$ soln. and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using 20%-35% EtOAc in hexane as the eluent to provide the coupled adduct **75(3)**.

(d) Synthesis of Compound **76(3)**: **75(3)** (1.0 mmol) is dissolved in a 50:50 mixture of CH_2Cl_2:TFA and the mixture is cooled to 0°C. After 30 min, the residue is concentrated to

remove the excess TFA and CH_2Cl_2 and the residue is rinsed with $CHCl_3$ and concentrated to remove any traces of TFA. The TFA amine salt is the one used in the general procedure for coupling a carboxylic acid and an amine, using an additional equivalent of NMM.
To the reaction mixture is added, a carboxylic acid or succinate ester of the acid (0.96 mmol), HOBt (130 mg, 0.96 mmol) and NMM (106 µl, 0.96 mmol). After cooling the mixture to 0°C, EDC (184 mg, 0.96 mmol) is added. The cold bath is removed after 10 min and the mixture is vigorously stirred to dissolve the remaining solid material. After stirring overnight, the reaction is quenched with 5% aqueous citric acid and Et_2O is added. The aqueous portion is extracted with Et_2O three times. The combined organic extracts are washed with sat. aqueous $NaHCO_3$ soln. and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to provide amide **76(3)**.
(e) Synthesis of Compound **77(3)**: To a stirred solution of **76(3)** (666 mg, 0.8 mmol) and $(Ph_3)_4Pd$ (336 mg, 1.28 mmol) in 20 ml of THF, is added H_2O (23 µl, 1.28 mmol). After stirring overnight, tlc analysis indicates the complete consumption of the starting material to provide **77(3)**.
(f) Synthesis of Compound **78(3)**: To a stirred 0°C solution of **77(3)** (1.0 mmol), HOBt (1.2 mmol), butyl amine (2.0 mmol) and NMM (2.5 mmol) in CH_2Cl_2 (0.5 M) is added EDC (1.3 mmol). After stirring overnight and subsequent warming to RT, sat. $NaHCO_3$ soln. and CH_2Cl_2 are added to the reaction mixture. The aqueous portion is extracted twice with CH_2Cl_2. The combined organic fractions are washed with 1N HCl and brine, dried over Na_2SO_4 and concentrated. The crude residue is purified by flash chromatography in silica gel using ethyl acetate/hexane as the eluent affording **78(3)**.
[Alternatively, the following amines can be used in the procedure: butyl amine, amyl amine, hexyl amine, heptyl amine, octyl amine, nonylamine, decylamine, undecylamine, dodecylamine, tridecylamine, 1-tetradecylamine, pentadecylamine, hexadecyl amine, octadecyl amine, 1-amino naphthalene, 2-amino naphthalene, 2-amino-2-naphthol perhydrochloride, 4-pentyl aniline, 4-hexyl aniline, 4-heptyl aniline, 4-octyl aniline, 4-decyl aniline, 4-dodecyl aniline, 4-tetradecyl aniline and 4-hexadecylaniline].

Example A38: Preparation of 81(3)

(a) Synthesis of compound **80(3)**: To a solution of **64(3)**



(2.11 mmol) in DMF (7 ml) is added 95% NaH (2.74 mmol) at 0°C under argon. After 30 min, the mixture is added 1-bromohexadecane (2.74 mmol; alternatively the alkyl halides and acid chlorides mentioned in Example A31(a) can be used in the procedure) followed by the addition of TBAI (2.74 mmol) and the resulting solution is warmed up to 25 °C overnight. The reaction is quenched by H_2O (10 ml), then extracted with EtOAc (3 x 10 ml) and the combined organic layers are washed with brine, dried with $MgSO_4$, filtered, evaporated and purified by column chromatography (hexane to EtOAc/hexane = 15 1/20) to yield **80(3)**.

(b) Synthesis of compound **81(3)**: To a solution of **80(3)** (1.62 mmol) in 1/1 acetone/H_2O (10 ml) is added NMO (0.24 g, 2.05 mmol) followed by a solution of OsO_4 in t-BuOH (0.2 g, 2.5% w/w) at 25 °C. The solution is stirred for 16 h and the reaction is quenched by the addition of $Na_2S_2O_3$ (0.2 g), Florisil (1 g) and H_2O (10 ml). The mixture is acidified to pH = 1 with 1 N HCl and the resulting solution is extracted with EtOAc (3 x 20 ml). The combined organic layers are washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and evaporated to yield a 1/1 mixture of diastereomeric diols.

To a solution of above diols in THF (8 ml) is added $NaIO_4$ (0.61 g) in one portion. The stirred slurry is added H_2O (8 ml) over 5 min and the mixture is kept stirring for 2 h. The resulting solution is extracted with EtOAc (3 x 20 ml) and the combined organic layers are washed with brine, dried with $MgSO_4$, filtered and evaporated to yield the crude aldehyde.

The above aldehyde is dissolved in acetone (7 ml) and the solution is cooled to 0°C. The mixture is added Celite (0.8 g) in one portion followed by the addition of Jones reagent drop by drop until a orange color persists. i-PrOH (1 ml) is added to quench any excess Jones reagent and the reaction mixture is then partitioned between EtOAc (50 ml) and 1 N HCl (50 ml). The aqueous layer is extracted with EtOAc (2 x 50 ml) and the combined organic phases are dried with ($MgSO_4$), concentrated and purified by silica gel flash chromatography (EtOAc/hexane/AcOH = 3/1/0.01) to yield the carboxylic acid.

To a solution of the above carboxylic acid (0.363 mmol) in CH_2Cl_2 (3 ml) is added BnO-Glu(OBn)-NH_2 • p-TsOH (200 mg, 0.399 mmol), triethylamine (56 µl, 0.399 mmol), HOBt (54.0 mg, 0.399 mmol) and EDC (76.4 mg, 0.399 mmol) at 25°C under argon. The

reaction is allowed to stir for 24 h before being diluted with CH_2Cl_2 (20 ml) and washed successively with a 1 N hydrochloric acid solution (15 ml), saturated $NaHCO_3$ solution (15 ml) and brine (15 ml). The organic phase is dried with $MgSO_4$, concentrated and purified by silica gel chromatoaraphy to yield **81(3)**.

Example A39: Preparation of compound 83(3)

(a) Synthesis of compound **82(3)**: The preparation from **80(3)** is followed by the procedure according to Example A38 using instead 3-carboxyethyl aniline to afford **82(3)**.

(b) Synthesis of compound **83(3)**: An ice-cold solution of 0.25 M LiOH in 75% $MeOH_{aq}$ (5.3 ml) is added to a solution of **82(3)** (230 mg, 0.27 mmol) in THF (4 ml) and the mixture is vigorously stirred for 2 days at 4°C. The resulting solution is acidified with 1 N HCl to pH 1-2 and extracted with EtOAc (3 x 10 ml). The combined organic layers are washed with brine, dried with $MgSO_4$, filtered, evaporated and purified by a short column chromatography to yield **83(3)**.

Example A40: Preparation of 83a(3)

Starting from **64(3)** and Br-$C_{16}H_{33}$ **83a(3)** is prepared according to Example A38.

Example A41: Preparation of 102i(3)

(a) Synthesis of C-allylmannose **107(3)**: To a solution of α-D-mannose pentaacetate (1.0 g, 2.56 mmol) at 0°C is added allyltrimethylsilane (1.22 ml, 7.69 mmol) followed by BF_3-Et_2O (1.5 ml, 12.8 mmol). The reaction mixture is allowed to warm to 23°C and TMSOTf (100 ml) is added and the solution is stirred for 24h. The mixture is poured into a saturated $NaHCO_3$ solution (50 ml) and the organic phase is diluted with CH_2Cl_2 (50 ml). The aqueous phase is extracted with CH_2Cl_2 (2 x 25 ml) and the combined organic phases are dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude oil which is used directly in the next step without further purification.

The prepared C-allylglycoside from above is dissolved at 23°C in anhydrous methanol (30 ml) and NaOMe (25 wt% in MeOH, 5 ml) is added. After 2 h the reaction mixture is quenched by the addition of Dowex resin (50W-X8). The resin is removed by filtration and the reaction mixture is concentrated under reduced pressure. The crude oil is purified by silica gel flash chromatography (CH_2Cl_2/MeOH, 9:1) giving tetraol **107(3)** as a mixture of α and β anomers (8:1).

(b) Synthesis of tetrabenzyl C-allylmannose: To a solution of **107(3)** (1.96 g, 9.61 mmol), BnBr (8 ml, 67.3 mmol), and TBAI (177 mg, 048 mmol) in THF (20 ml) at 0°C is added NaH (2.35 g, 57.6 mmol). The cooling bath is removed and the reaction mixture is allowed to stir for 24 h. The reaction is diluted with EtOAc (50 ml) and poured into a saturated NH_4Cl solution (50 ml). The aqueous phase is extracted with EtOAc (2 x 30 ml) and the combined organic phases are dried ($MgSO_4$) and concentrated under reduced pressure providing the crude oil. Purification by silica gel flash chromatography (hexane:EtOAc, 100% to 9:1 to 1:1) gives the desired product.

(c) Synthesis of tetrabenzyl carboxylic acid **108(3)**: To a solution of the above prepared terminal olefin (679 mg, 1.20 mmol) in CH_2Cl_2:MeOH (8 ml:4 ml) at -78°C is bubbled O_3 in O_2 until a blue color persists. To remove residual O_3, pure O_2 is bubbled through until the solution turns clear. DMS (1.7 ml, 24.0 mmol) is added and the reaction mixture is warmed to 23°C and stirred for 24 h. The reaction mixture is evaporated and partitioned between a saturated $NaHCO_3$ solution (50 ml) and EtOAc (5 ml). The aqueous phase is extracted with EtOAc (2 x 30 ml) and the combined organic phases are dried and concentrated under reduced pressure. The crude oil is used directly without further purification. The aldehyde prepared **109(3)** is further reacted according to the procedure described in Example A30(d) giving the carboxylic acid **108(3)**.

(d) To a solution of carboxylic acid **108(3)** (50 mg, 0 086 mmol), H-Gly-OBn • pTsOH (32 mg, 0.095 mmol; also HCl salts can be used in lieu of the pTsOH salt), HOBt hydrate (12.8 mg, 0.095 mmol), and NMM (10.3 ml, 0.095 mmol) in CH_2Cl_2 (500 ml) at 0°C is added EDC (18 mg, 0.095 mmol). The reaction is allowed to stir for 24 h before being diluted with CH_2Cl_2 (50 ml) and washed successively with a 5% citric acid solution (25 ml), saturated $NaHCO_3$ solution (25 ml), and brine (25 ml). The organic phase is dried ($MgSO_4$), concentrated under reduced pressure, and purified by silica gel chromatography (EtOAc:Hexane 1:1) giving **102l(3)**.

Example A42: Preparation of 103l(3)

103l(3) is prepared according to the procedure described in Example A41 coupling with BnO-Tyr-NH_2 • pTsOH.

Example A43: Preparation of 104l(3)

104l(3) is prepared according to the procedure described in Example A41 coupling with BnO-Glu(OBn)-NH_2 • pTsOH..

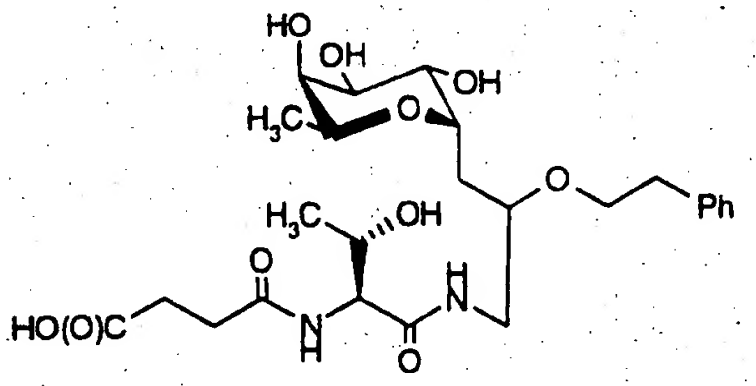
Example A44: Preparation of ethyl (2*S*,3*R*)-2,3-dihydroxy-4-(tetra-O-benzyl-α-D-mannopyranosyl)-butanoate 113(3)

To a suspension of LiCl (67 mg, 1.58 mmol) and triethyl phosphonoacetate (0.30 ml, 1.51 mmol) in dry CH_3CN (12 ml) is added DBU (185 µl, 1.24 mmol) followed by (2-(tetra-O-benzyl-α-D-mannopyranosyl)acetaldehyde **109(3)** (700 mg, 1.235 mmol) at 23°C and the reaction is stirred for 40 min. The mixture is taken up in ether, extracted with 0.5 N HCl, saturated $NaHCO_3$- sol. and brine, dried over $MgSO_4$. After removal of the solvent in vacuo the residue is purified by SGCC (20% EtOAc in hexanes) to give the desired α,β-unsaturated ester.

The α,β-unsaturated ester (211 mg, 331 µmol) is subjected to the general procedure described for the asymmetric dihydroxylation reaction (AD-reaction) to provide diol **113(3)**.

B Preparation of the mimetica

Example B1: Preparation of 1-(2-monosuccinamidyl-L-threonine)-2-2(2-phenethoxy)-3-(α-L-fucopyranosyl)propane 1 [1a (2'*R*); 1b (2'*S*)]

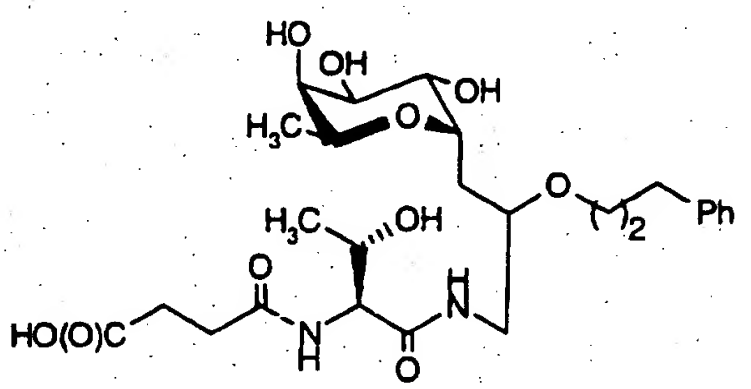


According to the general deprotection procedure A **25a** (33.7 mg, 34.5µmol) is deprotected and passed through the Anotop 25 membrane filter to give the title compound **1a** (16.3mg, 90%) as a white solid. The corresponding diastereomer is obtained similarly by deprotection of pentabenzyl derivative **25b** (47.0mg, 48.1µmol) to afford **1b** as a white solid. Data for **1a**: ^{1}H NMR (400 MHz, D_2O) δ 1.09 (3H, d, J = 6.4, Me-thr), 1.16 (3H, d, J = 6.3, H-6), 1.64 (1H, ddd, J = 14.5, 7.6, 4.1, H-1'a), 1.75 (1H, ddd, J = 15.0, 10.8, 4.6, H-1'b), 2.54-2.63 (4H, m, $HO_2CC\underline{H}_2C\underline{H}_2CONH$), 2.77-2.89 (2H, m, $OCH_2C\underline{H}_2Ph$), 3.22 (1H, br ddd, J = 13.8, 10.9, 5.4,

H-3'a), 3.41-3.49 (2H, m, H-2', OC<u>H</u>HCH$_2$Ph), 3.56 (1H, dt, J = 6.6, 6.0, H-3'b), 3.62 (1H, dd, J = 10.0, 3.3, H-3), 3.68 (1H, br d, J = 2.8, H-4), 3.73 (1H, dt, J = 9.9, 6.9, OCH<u>H</u>CH$_2$Ph), 3.85 (1H, dd, J = 9.8, 6.4, H-2), 3.86 (1H, m, H-5), 3.97 (1H, br ddd, J = 10.5, 5.9, 4.6, H-1), 4.16 (1H, dq, J = 6.4, 4.3, β-H-thr), 4.22 (1H, d, J = 4.1, α-H-thr), 7.25-7.38 (5H, m, aromatic), 7.90 (ca. 1H, t, J = 5.6, CON<u>H</u>CH$_2$); ^{13}C NMR (100 MHz, D$_2$O) δ 18.06, 21.28, 29.06, 33.22, 38.25, 44.05, 44.17, 61.66, 69.36, 69.71, 72.04, 73.30, 73.93, 74.82, 79.07, 128.95, 131.10, 131.48, 141.65, 174.68, 178.17, 180.91; HRMS calcd for CsC$_{25}$H$_{38}$N$_2$O$_{10}$ (M+Cs) 659.1581, found 659.1562.

Data for **1b**: ^{1}H NMR (400 MHz, D$_2$O) δ 1.15 (3H, d, J = 6.4, Me-thr), 1.18 (3H, d, J = 6.3, H-6), 1.54 (1H, br t, J = 11.6, H-1'a), 1.79 (1H, br t, J = 12.9, H-1'b), 2.58 (4H, s, HO$_2$CC<u>H$_2$</u>C<u>H$_2$</u>CONH), 2.87 (2H, t, J = 7.1, OCH$_2$C<u>H$_2$</u>Ph), 3.20 (1H, br dt, J = 13.7, 5.0, H-3'a), 3.39 (1H, br dt, J = 13.8, 4.7, H-3'b), 3.62 (1H, m, H-2'), 3.66 (1H, dd, J = 10.1, 3.0, H-3), 3.73 (1H, br d, J = 2.9, H-4), 3.77 (2H, br dt, J = 10.8, 6.8, OC<u>H$_2$</u>CH$_2$Ph), 3.88 (1H, dd, J = 10.0, 6.2, H-2), 3.91 (1H, m, H-5), 4.01 (1H, m, H-1), 4.19 (1H, d, J = 3.6, α-H-thr), 4.23 (1H, br dq, J = 6.4, 3.8, β-H-thr), 7.25-7.38 (5H, m, aromatic), 7.98 (ca. 1H, t, J = 5.7, CON<u>H</u>CH$_2$); ^{13}C NMR (100 MHz, D$_2$O) δ 18.05, 21,32, 29.23, 33.16, 38.02, 44.90, 45.01, 61.68, 69.24, 69.53, 69.95, 72.23, 73.45, 74.04, 74.14, 76.77, 128.92, 131.08, 131.39, 141.35, 174.87, 174.95, 178.22; HRMS calcd for NaC$_{25}$H$_{38}$N$_2$O$_{10}$ (M+Na) 549.2424, found 549.2412.

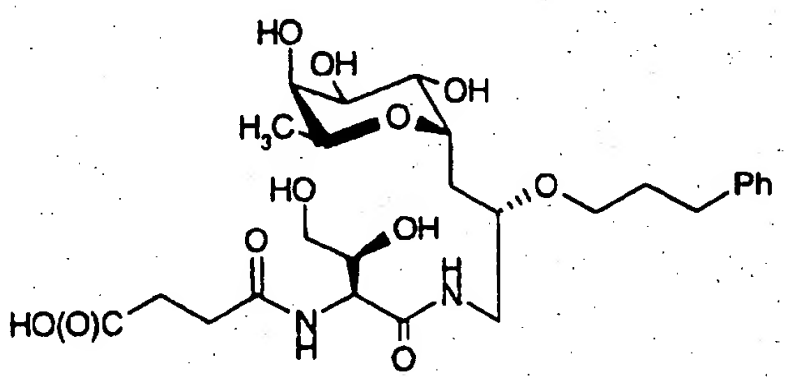
Example B2: Preparation of 1-(2-monosuccinamidyl-L-threonine)-2-(3-phenylprop-oxy)-3-(α-L-fucopyranosyl)propane [(2'*R/S*)] 2



Boc-carbamate **26** (94mg, 132μmol, 1:1 mixture of diastereomers) is deprotected according to the general procedure and the obtained free amine is treated with N-Boc-O-benzyl-L-threonine (45mg, 145μmol), EDC (29mg, 152μmol), HOBt (21mg, 157μmol) and NMM (32μl, 290μmol) in DCM (1.5ml) according to general procedure B for 7h to give the coupled

compound (101mg, 85%) as a white solid. Removal of the Boc group (general procedure) and subsequent treatment with monobenzyl succinate (26mg, 125µmol), EDC 25mg, 131µmol), HOBt (18.5mg, 137µmol) and NMM (20µl, 182 µmol) in DCM (1.3 ml) according to general procedure B for 12h yields the pentabenzyl compound (109mg, 98%) as a pale yellow oil. The benzyl groups are removed according to general procedure A, the product is filtered through the Anotop 25 membrance filter and 2 is after lyophilization obtained as a white solid (1:1 diastereomeric mixture. ^{1}H NMR (400 MHz, D_2O) δ 1.13-1.19 (6H, Me-thr, H-6), 1.61/1.75 (1H, m, H-1'a), 1.86 (3H, m, $OCH_2C\underline{H}_2CH_2Ph$, H-1'b), 2.57-2.67 (6H, m, $OCH_2CH_2C\underline{H}_2Ph$, $HO_2CC\underline{H}_2C\underline{H}_2CONH$), 3.28-4.28 (12H, m, H-1, 2, 3, 4, 5, 2', 3', α, β-H-thr, $OC\underline{H}_2CH_2CH_2Ph$), 7.28-7.36 (5H, m, aromatic); ^{13}C NMR (100 MHz, D_2O) δ 18.08, 21.26/21.35, 28.82, 33.03, 33.40, 33.89/33.98, 45.03, 61.69, 69.25/69.42, 69.56/69.81, 70.01, 71.33, 72.13, 72.27, 73.98, 75.11, 76.51, 78.58, 128.50, 131.02, 131.10, 139.85, 175.06, 177.90, 178.13; HRMS calcd for $CsC_{26}H_{40}N_2O_{10}$ (M+Cs) 673.1737, found 673.1712.

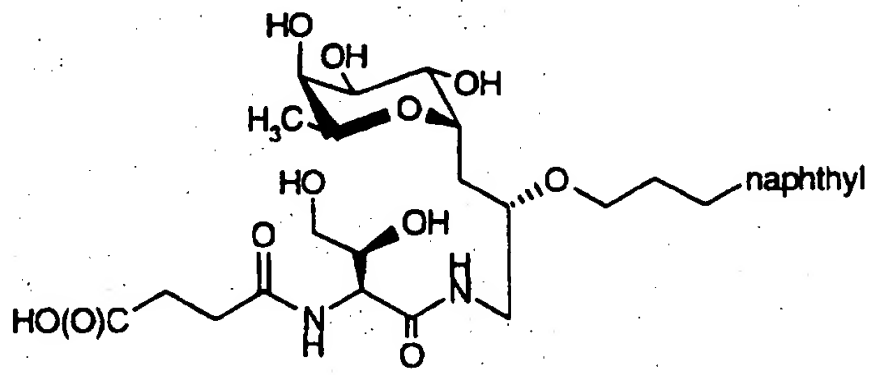
Example B3: Preparation of (2*S*)-1-{(2*S*,3*R*)-4-dihydroxy-2-monosuccinamidyl-butyr-amidyl}-2-(3-phenylpropoxy)-3-(α-L-fucopyranosyl)-propane 3b



According to the general deprotection procedure A **28b** (72.5 mg, 72 µmol) is deprotected and filtered through the Anotop 10 membrane filter to yield after lyophilization **3b** as a white solid. ^{1}H NMR (500 MHz, D_2O) δ 1.14 (3H, d, J = 6.4, H-6), 1.58 (1H, ddd, J = 14.8, 10.4, 2.7, H-1'a), 1.79-1.85 (3H, m, H-1'b, $OCH_2C\underline{H}_2CH_2Ph$), 2.46-2.56 (4H, m, $HO_2CC\underline{H}_2C\underline{H}_2CONH$), 2.63 (2H, t, J = 7.5, $OCH_2CH_2C\underline{H}_2Ph$), 3.29 (1H, dt, J = 14.3, 5.4, H-3'a), 3.33 (1H, dt, J = 13.9, 5.2, H-3'b), 3.48 (1H, dt, J = 13.9, 6.6, $OC\underline{H}HCH_2CH_2Ph$), 3.56 (1H, dd, J = 12.1, 6.1, γ-Ha-hthr), 3.57-3.73 (5H, m, H-3, 4, 2', $OCH\underline{H}CH_2CH_2Ph$, γ-Hb-hthr), 3.76 (1H, br q, J = 6.1, β-H-hthr), 3.92 (2H, m, H-2, 5), 4.13 (1H, ddd, J = 11.7, 6.0, 2.7, H-1), 4.37 (1H, d, J = 7.2, α-H-hthr), 7.19-7.33 (5H, m, aromatic), 8.14 (1H, t, J = 6.0, $CONH\underline{C}H_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.39, 27.62, 31.02, 31.70, 32.28, 43.16, 43.27,

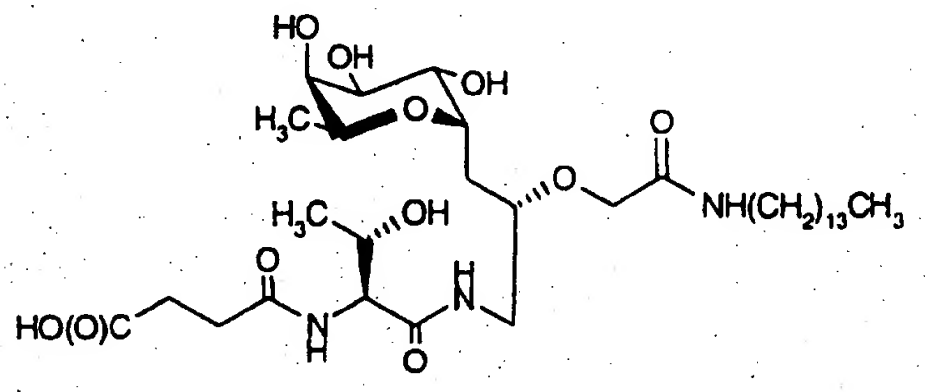
56.21, 63.14, 67.88, 68.33, 70.36, 70.56, 71.64, 72.33, 72.47, 74.84, 126.79, 129.32, 129.37, 134.01, 172.47, 172.55, 175.54; Electrospray-MS: calcd for $C_{26}H_{41}N_2O_{11}$ (M+H) 557, found 557, calcd for $C_{26}H_{39}N_2O_{11}$ (M-H) 555, found 555.

Example B3': Preparation of 4



4 is prepared according to Example B3 starting from the corresponding protected compound.

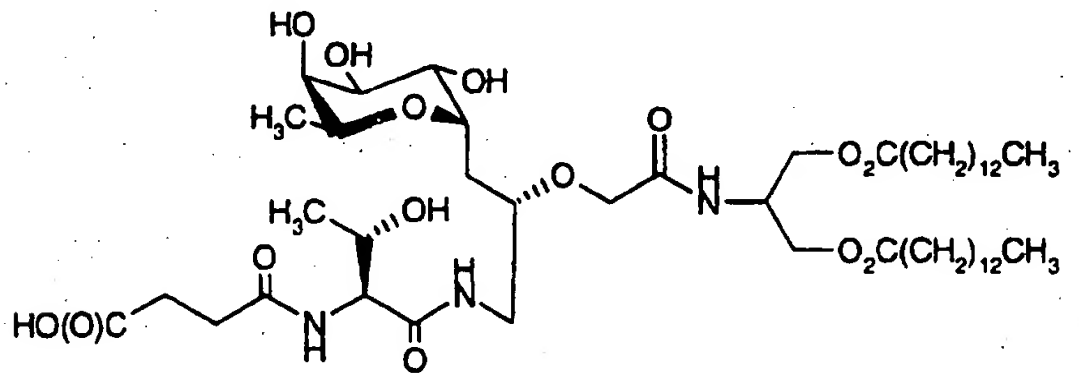
Example B4: Preparation of (2*S*)-1-(2-monosuccinamidyl-L-threonine)-2-(tetradecylaminocarbonylmethoxy)-3-(α-L-fucopyranosyl)propane 5b



32b (35.5mg, 31.5μmol) is deprotected according to the general procedure A to afford after filtration through the Anotop 25 membrane filter (MeOH) **5b** as a white solid. ^{1}H NMR (400 MHz, $CD_3OD/CD_3CO_2D/D_2O$ 25:5:1) δ 0.86 (3H, t, J = 7.0, $(CH_2)_{13}C\underline{H}_3$), 1.19 (3H, d, J = 6.3, Me-thr), 1.20 (3H, d, J = 6.3, H-6), 1.25 (22H, br s, $CH_2CH_2(C\underline{H}_2)_{11}CH_3$), 1.50 (2H, m, $CONHCH_2C\underline{H}_2(CH_2)_{11}$), 1.74 (1H, br ddd, J = 14.7, 9.9, 2.8, H-1'a), 1.87 (1H, br ddd, J = 14.4, 11.7, 2.7, H-1'b),2.54-2.73 (4H, m, $HO_2CC\underline{H}_2C\underline{H}_2CONH$), 3.21 (2H, dd, J = 7.4, 5.5, $CONHC\underline{H}_2CH_2$), 3.39 (2H, d, J = 5.0, H-3'), 3.64 (1H, m, H-2'), 3.66 (1H, dd, J = 9.7, 3.2, H-3), 3.71 (1H, br s, H-4), 3.79 (1H, br q, J = 6.3, H-5), 3.95 (1H, dd, J = 9.5, 5.9, H-2), 4.06 (1H, d, J = 15.2, $OC\underline{H}HCONH$), 4.12 (1H, d, J = 15.1, $OCH\underline{H}CONH$), 4,13 (1H, m, H-1), 4.26 (1H, d, J = 3.2, α-H-thr), 4.31 (1H, dq, J = 6.4, 3.3, β-H-thr); ^{13}C NMR (100 MHz,

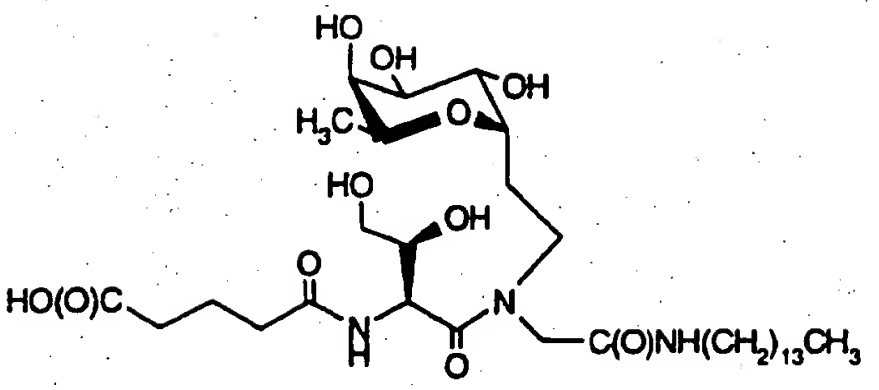
$CD_3OD/CD_3CO_2D/D_2O$ 25:5:1) δ 14.47, 16.77, 20.21, 23.57, 27.84, 28.41, 30.27, 31.34, 33.87, 40.12, 43.54, 60.38, 67.95, 68.70, 69.23, 71.74, 72.69, 72.76, 77.26, 172.87, 173.29, 175.62, 177.09,; HRMS calcd for $NaC_{33}H_{61}N_3O_{11}$ (M+Na) 676.4384, found 676.4380

Example B5: Preparation of (2*S*)-1-(2-monosuccinamidyl-L-threonine)-2-dimyristoyl-serinolcarbonylmethoxy)-3-(α-L-fucopyranosyl)propane 6b



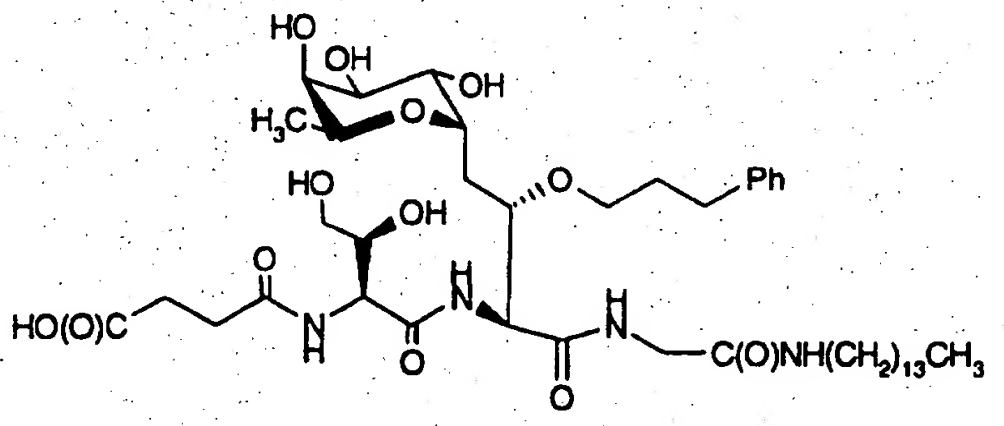
34b (32.8mg, 23.0μmol) is deprotected according to the general procedure A. The reaction is first filtered through a celite pad with H_2O to remove the transesterified side product (4.2mg). Afterwards, the filter cake is washed with MeOH, the solution is filtered through the membrane filter, the solvent is removed in vacuo and a emulsion of the remaining oil in H_2O is lyophilized to afford **6b** as a white solid. ^1H NMR (400 MHz, $CD_3OD/CD_3CO_2D/D_2O$ 25:5:1) δ 0.80 (6H, t, J = 6.6, $(CH_2)_{12}C\underline{H}_3$), 1.11 (3H, d, J = 4.9, Me-thr), 1.13 (3H, d, J = 5.9, H-6), 1.19 (4 OH, s, $(C\underline{H}_2)_{10}CH_3$), 1.51 (4H, br t, J = 6.2, $O_2CCH_2C\underline{H}_2(CH_2)_{10}CH_3$), 1.67 (1H, br t, J = 11.9, H-1'a), 1.79 (1H, br t, J = 12.2, H-1'b), 2.27 (4H, t, J = 7.4, $O_2CC\underline{H}_2(CH_2)_{11}CH_3$), 2.46-2.63 (4H, m, $HO_2CC\underline{H}_2C\underline{H}_2CONH$), 3.30 (2H, m, H-3'), 3.56-3.63 (4H, m, H-2, 3, 4, 2'), 3.70 (1H, br q, J = 6.5, H-5), 3.86 (1H, dd, J = 9.3, 5.7, H-1), 4.02 (1H, d, J = 15.4, $OC\underline{H}HCONH$), 4.08 (1H, d, J = 15.4, $OCH\underline{H}CONH$), 4.12 (4H, br dd, J = 5.1, 4.2, $CONHCH(C\underline{H}_2O_2CR)_2$), 4.19 (1H, d, J = 2.8, α-H-thr), 4.24 (1H, dq, J = 6.2, 3.0, β-H-thr), 4.36 (1H, qui, J = 5.8, $CONHC\underline{H}(C\underline{H}_2O_2CR)_2$), HRMS calcd for $NaC_{50}H_{91}N_3O_{15}$ (M+Na) 996.6348, found 996.6368.

Example B6: Preparation of 1-{(2*S*,3*R*)-3,4-dihydroxy-2-monoglutaramidyl-butyr-amidyl}-N-(tetradecylaminocarbonylmethyl)-2-(α-L-fucopyranosyl)-ethane 7



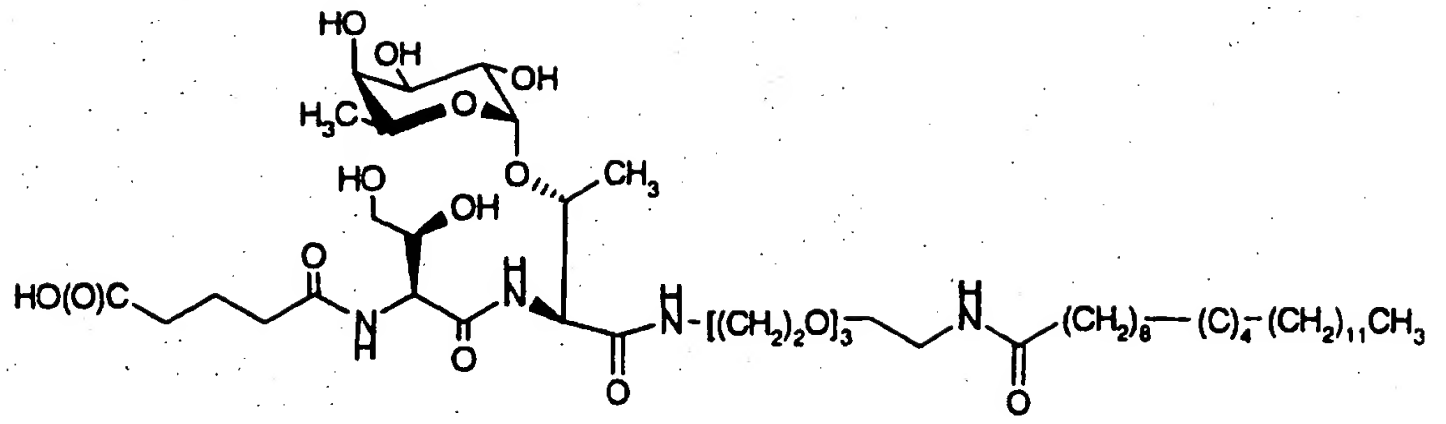
According to the general deprotection procedure A **39** (56mg, 50µmol) is deprotected and filtered through the Anotop 25 membrane filter to yield **7** after lyophilization as a white solid. (NMR spectra at 23°C show rotamers, several peaks are doubled or broadened.) ^{1}H NMR (400 MHz, D_2O) δ 0.85 (3H, br s, $(CH_2)_{13}C\underline{H}_3$), 1.25 (25H, br s, H-6, $(C\underline{H}_2)_{11}CH_3$), 1.48 (2H, br s, $CONHCH_2C\underline{H}_2$), 1.86-2.32 (8h, br m, $HO_2C(C\underline{H}_2)_3CONH$, H-1'), 3.16-4.18 (15H, br m, H-1, 2, 3, 4, 5, 2', α, β, γ-H-hthr, $NC\underline{H}_2CONHC\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) α 16.34, 18.51, 23.70, 25.13, 29.54, 31.48, 32.02, 32.48, 34.48, 37.03, 42.06, 49.10, 52.47, 64.73, 69.72, 69.98, 72.46, 74.22, 74.32, 75.97, 172.07, 175.17, 177.81, 179.36/180.13; HRMS calcd for $CsC_{33}H_{61}N_3O_{11}$ (M+Cs) 808.3360, found 808.3368.

Example B7: Preparation of compound 8



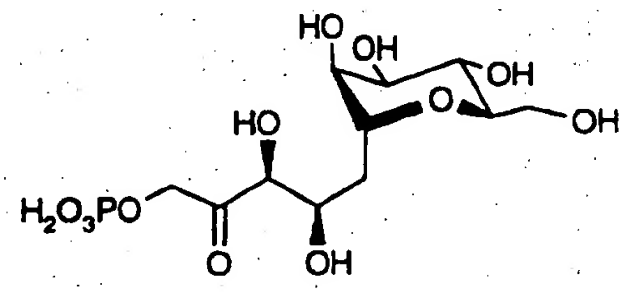
According to the general deprotection procedure A **47** (56mg, 50µmol) is deprotected and filtered through the Anotop 25 membrane filter to yield **8**.

Example B8: Preparation of compound 58



To a suspension of **54** (31mg, 0.05mmol) in DMF (2.5ml) and Et_3N (0.26ml) is added **57** (24mg, 0.05 mmol) at 0°C. The mixture is stirred for 30 min. at 0°C and 48h at RT. The solvent is removed in vacuo and the residue is dissolved in AcOEt (20ml) and washed with water. The organic layer is dried over $MgSO_4$ and evaporated in vacuo. The residue is purified by gel-filtration on a Sephadex LH-20 column eluting with $CHCl_3$: MeOH (1.1) to obtain **58**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (br, 1H), 7.94 (br, 1H), 7.51 (br, 1H), 6.63 (br, 1H), 4.94 (br, 1H), 4.65-4.53 (m, 3H), 3.89-3.43 (m, 23H), 2.36 (br, 4H), 2.24 (t, J = 7.0 Hz, 4H), 2.18 (t, J = 7.5 Hz, 2H), 1.92 (br, 2H), 1.59 (br, 2H), 1.54-1.47 (m, 4H), 1.36-1.11 (m, 26 H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 1.74.1, 174.0, 172.5, 169.8, 77.6, 77.4, 70.2, 69.8, 65.3, 65.2, 39.1, 36.5, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.8, 28.8, 28.3, 25.7, 22.7, 19.2, 16.2, 14.7, 14.1; MS m/e calcd for $C_{52}H_{90}N_4O_{16}Cs$ (M+Cs$^+$): 1159.5406, found 1159.5438.

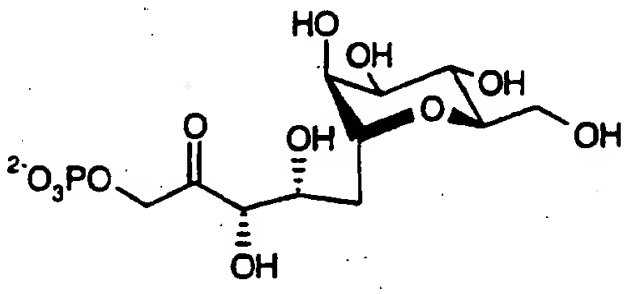
Example B9: Preparation of 6(14)



1.2 mmol (270mg) of aldehyde **5(14)** are dissolved in DHAP (1mmol, 3.2ml of a 314 mM solution). The pH is adjusted to 6.8 by adding NaOH and 400 u of FDP aldolase (Sigma) are added. After overnight period the pH is adjusted to 7.5 and 1g of $BaCl_2 \cdot 2\ H_2O$ (4.4 mmol) in 5 ml of water is added slowly. The cloudy mixture is kept in an ice bath for 15 min. and the precipitates are removed by centrifugation. To the supernatant 2 volumes of acetone are added and the mixture is stored at 0°C for 1 h. The precipitates are collected by centrifugation and the supernatant is discarded. The pellet is treated with Dowex-50 H$^+$ until

the solid is completely dissolved, and the resin is filtered off. The pH of the filtrate is adjusted to 7.0 by adding NaOH. Lyophilization yields the C-glycosyl phosphate **6(14)** as sodium salt.

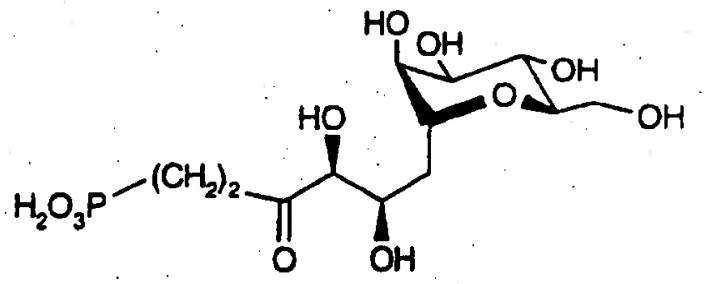
Example B9': Preparation of 4a(3)



4a(3)

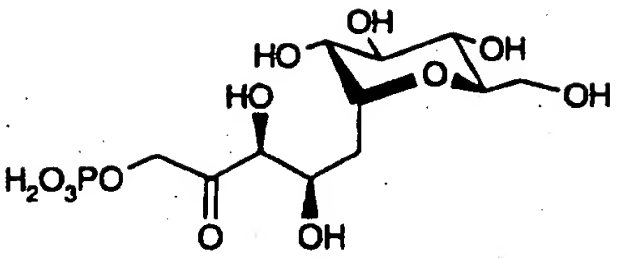
According to Example B9 **4a(3)** is prepared: ^{1}H NMR (D_2O, 400 MHz) δ 4.55 (dd, J=18.7, 6 Hz, 1H), 4.45 (dd, J=18.7, 6, 1H), 4.33 (d, J=2 Hz, 1H), 4.28 (ddd, J=10.4, 3, 2 Hz, 1H), 4.20 (ddd, J=11.5, 3.6, 2 Hz, 1H), 3.77 (dd, J=3.3, 9.3 Hz, 1H), 3.74 (dd, J=12.1, 5.8 Hz, 1H), 3.67 (dd, J=9.3, 3.3 Hz, 1H), 3.56 (dd, J=12.1, 5.8 Hz, 1H), 3.48 (t,J=9.3 Hz, 1H), 3.42 (ddd, J=9.3, 5.8, 2.2 Hz, 1H), 1.92 (ddd,J=14.7, 11.5, 3 Hz,1H), 1.60 (ddd, J=14.7, 10.4, 3.6 Hz, 1H) ppm;^{13}C NMR (D_2O,100 MHz), δ 212.60, 78.13, 75.11, 73.97, 72.09, 70.86, 68.40, 68.20, 67.65, 61.47, 30.49 ppm.

Example B10: Preparation of Compound 7(14)



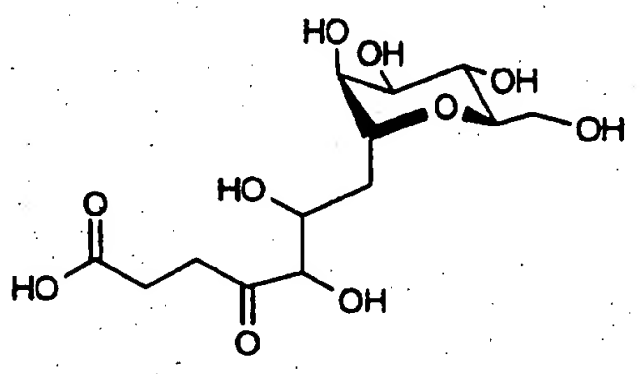
Starting from **5(14)** and C-DHAP [Fessner et al. Angew. Chem. Int. Ed. Eng. 33:209 (1994); Arth et al. Liebigs Ann., 2037 (1995)] (1mmol, 3ml of a 330 mM solution) **7(14)** is prepared in analogy to Example B9.

Example B11: Preparation of Compound 13(14)



Starting from **12(14)** and DHAP **13(14)** is prepared in analogy to Example B9.

Example B12: Preparation of (2*S*,3*R*)-N-carboxylmethyl-2,3-dihydroxy-4-(α-D-manno-pyranosyl)-butyramide 5(15)



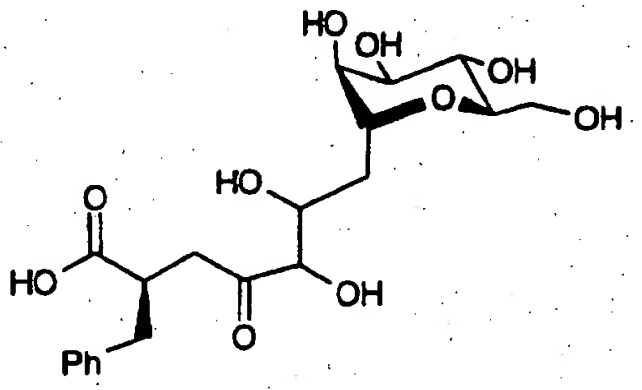
An ice-cold solution of LiOH (20 ml, 0.25 M in MeOH/H_2O 3:1) is added to **13(15)** (ethyl (2*S*,3*R*)-2,3-dihydroxy-4-(tetra-O-benzyl-α-D-mannopyranosyl)-butanoate) prepared from 2-(tetra-O-benzyl-α-D-mannopyranosyl)acetaldehyde according to Blanchette et al. [Tetrahedron Lett. 2183 (1984)] (1 mmol) at 0°C and vigorous stirring is continued for 2 days at 4°C. The reaction mixture is acidified with cold 1 N HCl to pH 1-2 and quickly extracted with EtOAc, washed with brine and dried over $MgSO_4$. The solvent is removed in vacuo to give the pure acid (A) as a slightly yellow oil.

According to the general procedure B for peptide coupling, the above carboxylic acid (50 mg, 78 µmol) and H-Gly-OBn • p-TsOH (30 mg, 89 µmol) are treated with EDC (18 mg, 94 µmol), HOBt (12 mg, 92 µmol) and NMM (9.5 ml, 86 µmol) in DCM (0.9 ml) for 6 h to obtain the desired amide (53 mg, 86%) as a pale yellow oil.

According to the general procedure A for hydrogenation of benzyl ethers, the above penta-benzyl compound (52.5 mg, 66.5 µmol) is deprotected and subsequently filtered through the Anotop 10 (0.02 µm) filter to yield polyhydroxyl compound **5(15)** after lyophilization as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 1.70 (1H, ddd, J = 14.2, 10.4, 3.1, H-1'a), 2.08 (1H, m, H-1'b), 3.53 (1H, ddd, J = 9.4, 6.0, 1.6, H-5), 3.64 (1H, t, J = 9.4, H-4), 3.71 (1H, dd, J = 12.1, 6.3, H-6a), 3.80 (1H, dd, J = 9.3, 3.2, H-3), 3.86 (1H, dd, J = 12.2, 1.9, H-6b), 3.90 (1H, dd, J = 2.9, 1.7, H-2), 3.94 (1H, d, J = 17.9 gly-Ha), 4.04 (1H, d, J = 17.8, gly-Hb), 4.06-

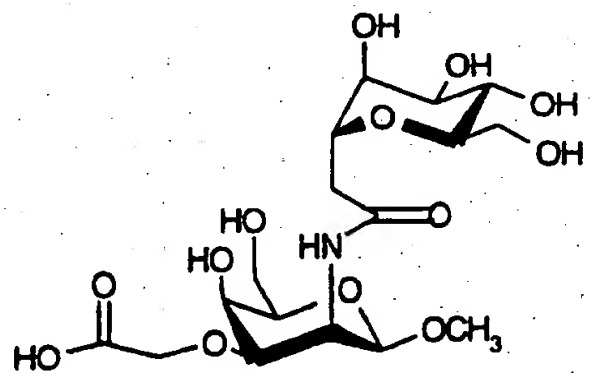
4.15 (2H, m, H-1, 2'), 4.16 (1H, d, J = 2.6, H-3'); ^{13}C NMR (100 MHz, D_2O) δ 33.05, 44.7 (br), 63.75, 69.84, 70.68, 73.17, 74.34, 76.17, 76.78, 77.29, 175.7 (br), 177.61; ESI MS calcd for $C_{12}H_{21}NO_{10}$ (M) 339, found (pos.: $M+H^+$) 340, (neg.: $[M-H]^-$) 338.

Example B13: Preparation of (2*S*,3*R*)-N-(benzyl-L-phenylalaninyl)-2,3-dihydroxy-4-(α-D-mannopyranosyl)-butyramide 6(15)



Starting from carboxylic acid A (51 mg, 79 µmol) and H-Phe-OBn-HCl (26 mg, 89 µmol) compound **6(15)** is prepared in analogy with Example B12. ^{1}H NMR (500 MHz, D_2O) δ 1.47 (1H, br t, J = 11.5, H-1'a), 1.89 (1H, br t, J = 12.9, H-1'b), 3.02 (1H, br s, β-Ha-phe), 3.13 (1H, br d, J = 10.8, β-Hb-phe), 3.40 (1H, dd, J = 7.3, 7.0), 3.54 (1H, t, J = 9.3), 3.62, (1H, dd, J= 11.7, 5.9), 3.68 (1H, br d, J = 7.0), 3.76 (1H, d, J = 11.3), 3.77 (1H, m), 3.93 (1H, br d, J = 7.7), 4.01 (1H, d, J = 11.1), 4.00-4.03 (1H, m), 4.54 (1H, br s), 7.19-7.29 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.17, 37.63, 62.09, 68.20, 68.86, 71.50, 72.64, 74.87, 75.58, 127.85, 129.46, 130.14, 137.57, 174.94 (br); HRMS calcd for $NaC_{19}H_{27}NO_{10}$ (M+Na) 452.1533, found 452.1545.

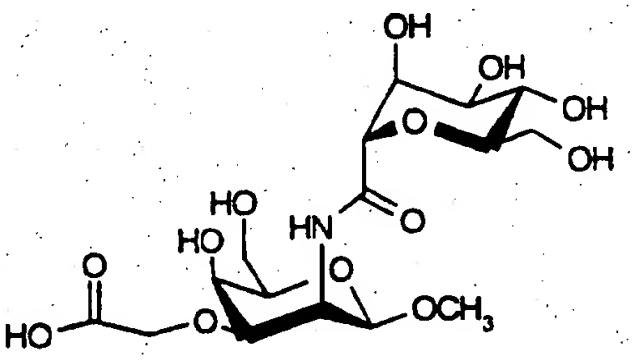
Example B14: Preparation of compound 19(15)



To a solution of **18(15)** (81 mg, 0.089 mmol) in 80% HOAc/water is added a catalytic amount of Pd/C (Degussa type, 10% by wt). The solution is flushed with hydrogen for 30

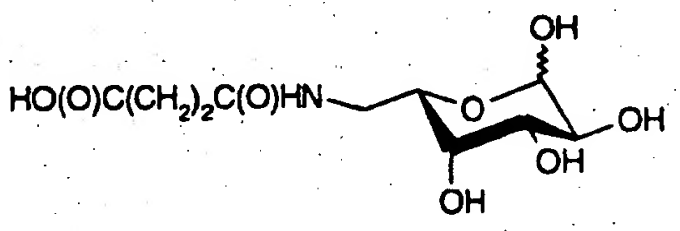
min then stirred for 24 h under a H_2 atmosphere. The reaction mixture is filtered through Celite and evaporated down under reduced pressure. The crude oil is further evaporated with H_2O (2 x 5 ml) and finally lyophilized giving **19(15)** as a white hygroscopic solid: 1H NMR (D_2O, 400 MHz) δ 4.56-4.55 (m, 2 H), 4.40-4.30 (m, 1 H), 4.50-3.55 (m, 13 H), 3.52 (s, 3 H), 2.83 (dd, J = 9.8, 15.8 Hz, 1 H), 2.61 (dd, J = 5.2, 15.7 Hz, 1 H); electrospray MS calcd for $C_{17}H_{28}O_8N$ (M - H), 454, found 454.

Example B15: Preparation of compound 24(15)



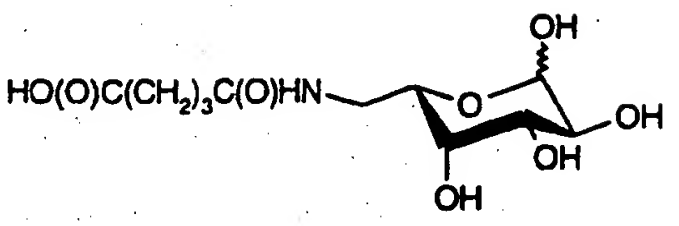
To a solution of **23(15)** (33 mg, 0.037 mmol) in 80% HOAc/water (10 ml) is added a catalytic amount of Pd/C (Degussa type, 10% by wt). The solution is flushed with hydrogen for 30 min then stirred for 24h under a H_2 atmosphere. The reaction mixture is filtered through Celite and evaporated down under reduced pressure. The crude oil is further evaporated with water (2 x 15 ml) and finally lyophilized giving **24(15)**: ^{1}H NMR (D_2O, 400 MHz) δ 8.02 (d, J = 7.6 Hz, 1 H), 4.58 (s, 2 H), 4.51 (s, 1 H), 4.48 (s, 1 H), 4.24-4.16 (m, 2 H), 4.07 (s, 1 H), 3.84-3.73 (m, 6 H), 3.62 (dd, J = 3.2, 4.0 Hz, 1 H), 3.55-3.45 (m, 5 H).

Example B16: Preparation of Compound 27(15)



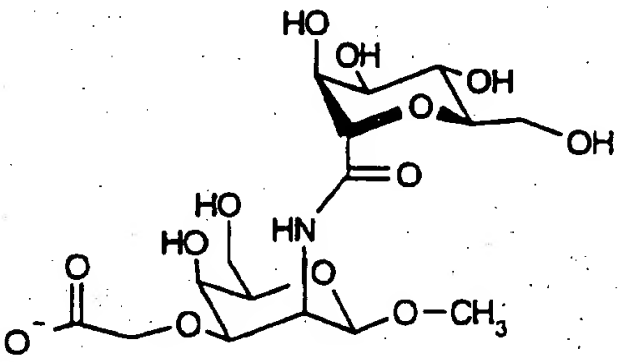
26(15) (61 mg, 0.169 mmol) is dissolved in 90% TFA:water (3 ml) and stirred for 4 h. The reaction mixture is evaporated down under reduced pressure and any residual TFA is removed by two co-evaporations with toluene (2 x 25 ml). The crude mimic is dissolved in water (10 ml), filtered, and lyophilized giving **27(15)**: HRMS calcd for $C_{10}H_{18}O_8N$ (M + H), 280.1032, found 280.1038.

Example B17: Preparation of Compound 29(15)



Starting from **28(15) 29(15)** is prepared in analogy to Example B16. HRMS calcd for $C_{11}H_{20}O_8N$ (M + H), 294.1189, found 294.1184.

Example B20: Preparation of methyl-2-[N-(2,3,4,6-hydroxy-α-D-mannopyranoside) carbonyl]amino-3-[(2-aceticacid)oxy]-4,6-hydroxy-galactopyranoside 1(3)

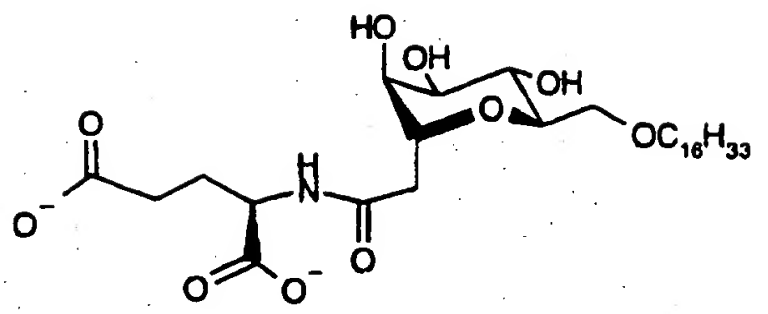


1(3)

Starting from a solution of **13(3)** (100 mg, 0.119 mmol) in CH_2Cl_2 (10 ml) the corresponding carboxylic acid is prepared according to Example A30(d).

To a solution of the above protected mimic (33 mg, 0.037 mmol) in 80% HOAc/H_2O (10 ml) is added a catalytic amount of Pd/C (Degussa type, 10% by wt). The solution is flushed with hydrogen for 30 min then stirred for 24 h under a H_2 atmosphere. The reaction mixture is filtered through Celite and evaporated down under reduced pressure. The crude oil is further evaporated with H_2O (2 x 15 ml) and finally lyophilized giving **1(3)**: ^{1}H NMR (D_2O, 400 MHz) δ 8.02 (d, J = 7.6 Hz, 1 H), 4.58 (s, 2 H),4.51 (s, 1 H), 4.48 (s, 1 H), 4.24-4.16 (m, 2 H), 4.07 (s, 1 H), 3.84-3.73 (m, 6 H), 3.62 (dd, J = 3.2, 4.0 Hz, 1 H), 3.55-3.45 (m, 5 H).

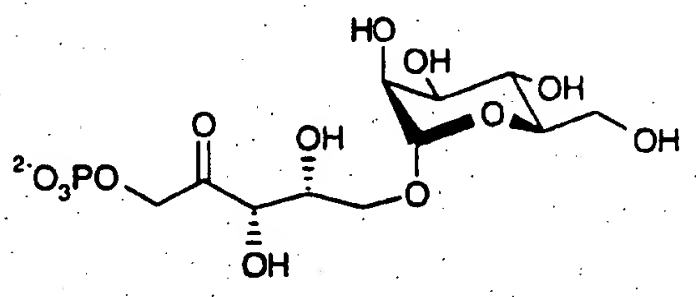
Example B 21: Preparation of N-[1-(6-O-hexadecanyl-α-D-mannopyranosyl)]acetyl-L-glutamic acid 3(3)



3(3)

To a mixture of **17(3)** (250 mg, 0.24 mmol) in HOAc/THF/H_2O (12 ml, 4/1/1) is added a catalytic amount of Pd/C (Degussa type, 10% by wt). The solution is flushed with hydrogen for 30 min then stirred for 24 h under a H_2 atmosphere. The reaction mixture is filtered and co-evaporated with toluene under reduced pressure. The crude product is recrystallized from chloroform and hexane to yield **3(3)**: ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1/1) δ 4.52-4.48 (m, 1H), 4.30-4.26 (m, 1 H), 3.76-3.69 (m, 6 H), 3.50 (t, J = 7.0 Hz, 2 H), 2.67 (dd, J = 14.9, 8.2 Hz, 1 H), 2.57 (dd, J = 14.9, 5.8 Hz, 1 H), 2.44-2.40 (m, 2 H), 2.26-2.22 (m, 1 H), 2.05-1.98 (m, 1 H), 1.59-1.56 (m, 2 H), 1.27 (bs, 26 H), 0.89 (t, J = 6.9 Hz, 3H); HRMS (FAB, M+Na) calcd for $C_{29}H_{53}NO_{10}Na$ 598.3567, found 598.3576.

Example B22: Preparation of 4(3) (Enzymatic aldol reaction)



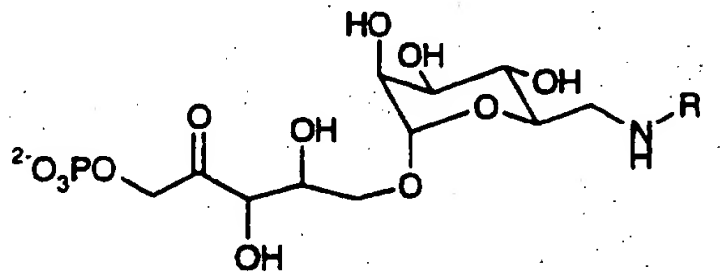
4(3)

1.2-1.5 mmol of **18(3)** is dissolved in a solution of DHAP, (1 mmol, 3 ml of a 330 mM solution). The pH is adjusted to 6.7 by adding NaOH and 200 u of FDP aldolase (Sigma) is added. After DHAP has been consumed (UV assay) and ^{31}P-NMR shows the appearance of a new product, the pH is adjusted to 8 and 1g of $BaCl_2 \cdot 2\ H_2O$ (4.4 mmol) in 5 ml of water is added slowly. The cloudy mixture is kept in an ice bath for 15 min and the precipitates are removed by centrifugation. Two volumes of acetone are added to the supernate and the mixture is stored at 0°C for 1 h. The precipitates are collected by centrifugation and the supernatant is discarded. The pellet is treated with Dowex-50 H^+ until the solid is completely dissolved (ca. 30min), and the resin is filtered off. The pH of the filtrate is adjusted to 7.0 by adding NaOH. Lyophilisation of the solution yields a mixture of the phosphonates that are further separated by ion exchange (HCO_3-column, 400mM of Et_3NH-HCO_3), converted to the H^+ form (Dowex-50 H^+) and lyophilized to yield **4(3)**. ^{1}H NMR (D_2O, 400 MHz) δ 4.72 (d,

J=1.7 Hz,1H), 4.69 (dd, J=18.4, 6.7 Hz, 1H), 4.54 (dd, J=18.4, 6.7 Hz, 1H), 4.41 (J=3 Hz, 1H), 4.15 (m, J=8.7, 5.7, 3 Hz, 1H), 3.83 (dd,J=3.3, 1.7 Hz, 1H), 3.75-3.65 (m, 3H, 3.60 (m, 2H), 3.55-3.45 (m, 2H) ppm; ^{13}C NMR (D_2O,100 MHz), δ,206.07, 96.49, 76.71, 73.72, 71.11, 70.94, 70.71, 69.18, 68.04, 65.71, 61.73 ppm.

Example B23: Preparation of Compounds of Table 1(3)

Table 1(3):

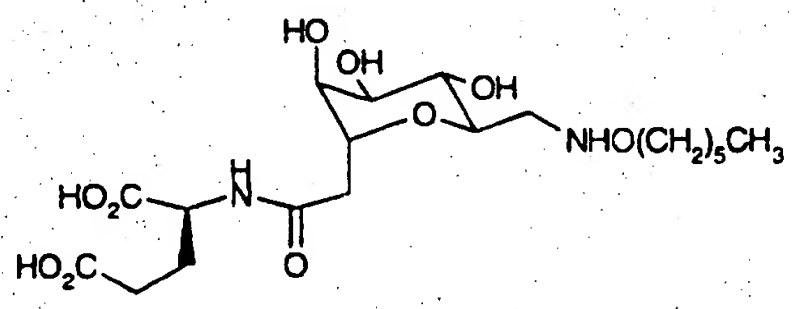


Compound	R	Compound	R
39(3)	$-C(O)(CH_2)_6CH_3$	50(3)	$-C(O)(CH_2)_{17}CH_3$
40(3)	$-C(O)(CH_2)_7CH_3$	51(3)	$-C(O)(CH_2)_{18}CH_3$
41(3)	$-C(O)(CH_2)_8CH_3$	52(3)	$-C(O)(CH_2)_{19}CH_3$
42(3)	$-C(O)(CH_2)_9CH_3$	53(3)	$-C(O)(CH_2)_{20}CH_3$
43(3)	$-C(O)(CH_2)_{10}CH_3$	54(3)	$-C(O)(CH_2)_{21}CH_3$
44(3)	$-C(O)(CH_2)_{11}CH_3$	55(3)	$-C(O)(CH_2)_{22}CH_3$
45(3)	$-C(O)(CH_2)_{12}CH_3$	56(3)	$-C(O)(CH_2)_5NHCO(CH_2)_3C(O)OH$
46(3)	$-C(O)(CH_2)_{13}CH_3$	57(3)	$-C(O)(CH_2)_5C_6H_5$
47(3)	$-C(O)(CH_2)_{14}CH_3$	58(3)	$-C(O)(CH_2)_3CONHCONH(CH_2)_{13}CH_3$ $CH_2CONH(CH_2)CH_3$
48(3)	$-C(O)(CH_2)_{15}CH_3$	58a(3)	$-(CH_2)_{15}CH_3$
49(3)	$-C(O)(CH_2)_{16}CH_3$	58b(3)	$-CH_2C_{10}H_7$
		58c(3)	$-(CH_2)_3C_6H_5$

Compound **63(3)** is dissolved in a mixture of THF/water (1/1) solution and hydrogenated at 1 atm in the presence of a catalytic amount of Pd/C. After stirred at RT for 6 h, the reaction mixture is filtered off using celite pad. The solvent is removed under vacuum to give free amine compound which can be used in the next step without further purification.

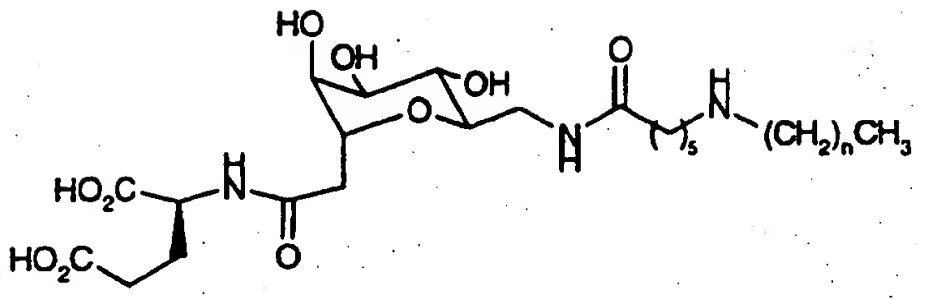
To a suspension of above amine in DMF (.10 M) is added OSu activated ester, RCOOSu (1.1 equivalents; R is a radical derived from the following acids; the activated ester is derived by reacting 1.1 equivalents of succinic anhydride with 1.0 equivalents of the following commercially available acids in 0.10 M methylene chloride at 0°C for 6 h: the acids are as follows: hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, palmitic acid, heptadecanoic acid, stearic acid, nonadecanoic acid, eicosanoic acid, hexaicosanoic acid, docosanoic acid, tricosanoic acid, tetracosanoic acid, hexacosanoic acid, heptacosanoic acid, octacosanoic acid, triacontanoic acid, 4-phenylbutyric acid, 5-phenyl valeric acid, 6-phenyl hexanoic acid, oleic acid, 3-trans-7-trans-farnesoic acid, 8-trans-10-trans-dodecandien-1-carboxylic acid, 2-naphthanoic acid, 1-hydroxy-2-naphthanoic acid, 1,4-dihydroxy-2-naphthanoic acid) at 0°C. The mixture is stirred overnight at 0°C. The solvent is removed in vacuo and the residue is dissolved in water (and washed with ether. The water layer is lyophilized to obtain compounds **39(3)** to **58c(3)**.

Example B24: Preparation of 69(3)



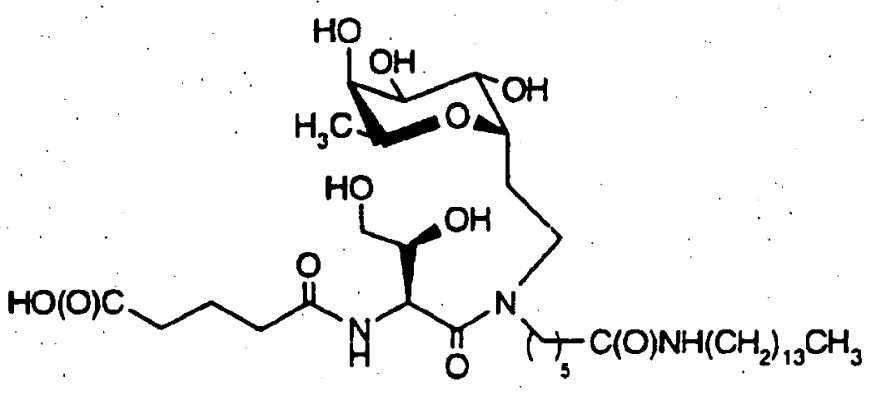
To a stirred solution of **68(3)** in 2 ml of HOAc are added 2 drops of H_2O, a catalytic amount of 10% Pd/C and H_2 gas. After stirring for 1 day, the catalyst is filtered off through a pad of celite and the pad is rinsed with HOAc. The filtrate is concentrated under reduced pressure to provide a white solid or a colorless oil. After lyophilization this product is a white hygroscopic solid **69(3)**.

Example B25: Preparation of 72(3)



The Boc compound **71(3)** (1.0 mmol) is dissolved in a 50:50 mixture of CH_2Cl_2:TFA and the mixture is cooled to 0°C. After 30 min, the residue is concentrated to remove the excess TFA and CH_2Cl_2 and the residue is rinsed with $CHCl_3$ and concentrated to remove any traces of TFA. The TFA amine salt is the one used in the general procedure for coupling a carboxylic acid and an amine, using an additional equivalent of NMM. To a stirred 0°C solution of the succinate ester of carboxylic acid RCO_2Su, (1.0 mmol) (the activated ester is derived by reacting 1.1 equivalents of succinic anhydride with 1.0 equivalents of an acid in 0.10 molar methylene chloride at 0°C for 6 h: useful acids are mentioned in example B 23), HOBt (1.2 mmol), the amine (2.0 mmol) and NMM (2.5 mmol) in CH_2Cl_2 (0.5 M) is added EDC (1.3 mmol). After stirring overnight and subsequent warming to RT sat. $NaHCO_3$ soln. and CH_2Cl_2 are added to the reaction mixture. The aqueous portion is extracted twice with CH_2Cl_2. The combined organic fractions are washed with 1N HCl and brine, dried over Na_2SO_4 and concentrated. The crude residue is purified by flash chromatography in silica gel using ethyl acetate/hexane as the eluent to afford compound **72(3)**.

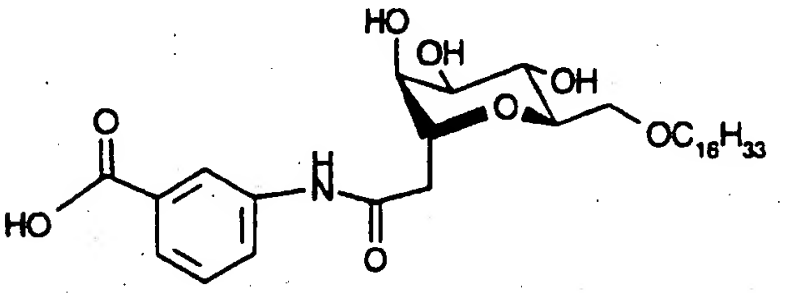
Example B26: Preparation of 79(3)



To a stirred solution of the amide **78(3)** in 2 ml of HOAc are added 2 drops of H_2O, a catalytic amount of 10% Pd/C and H_2 gas. After stirring for 1 day, the catalyst is filtered off through a pad of celite and the pad is rinsed with HOAc. The filtrate is concentrated under reduced pressure to provide a white solid or a colorless oil. After lyophilization this product is a white hygroscopic solid **79(3)**.

Example B29: Preparation of 3-{N-[1-(6-O-Hexadecanyl-α-D-mannopyranosyl)]-acetyl)aminobenzoic acid 3a(3)

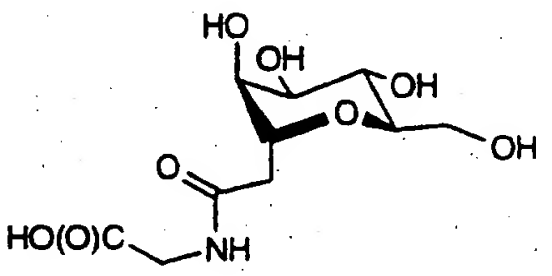
The preparation from **83a(3)** is followed by the procedure according to Example B27 to afford **3a(3)**.



3a(3)

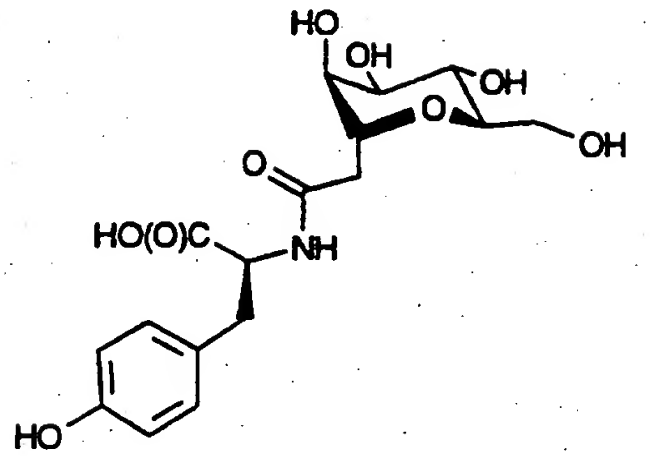
^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1/1) δ 8.16 (s, 1H), 7.87 (d, J = 7.6 Hz, 1 H), 7.78 (d, J = 7.6 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 4.39-4.36 (m, 1 H), 4.10 (s, 1 H), 3.82-3.64 (m, 5 H), 3.47 (t, J = 7.1 Hz, 2 H), 2.81 (dd, J = 15.1, 9.9 Hz, 1 H), 2.67 (dd, J = 15.1, 4.6 Hz, 1 H), 1.44-1.18 (m, 28 H), 0.89 (t, J = 6.8 Hz, 3 H); HRMS (FAB, M+Cs) calcd for $C_{31}H_{53}NO_8Cs$ 698.2669, found 698.2684.

Example B30: Preparation of 102(3)



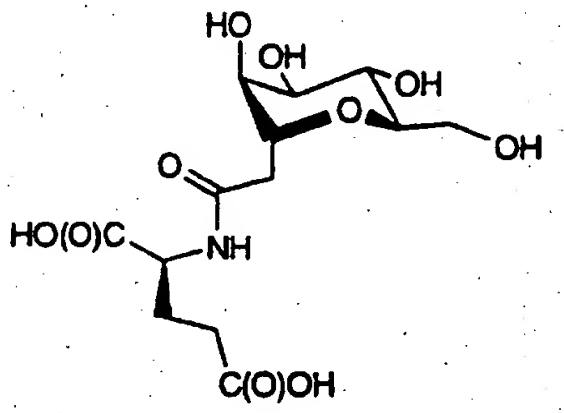
To a solution of **102l(3)** (33 mg, 0.045 mmol) in 80% acetic acid/H_2O is added a catalytic amount of Pd/C (Degussa type, 10% by wt; Aldrich). The solution is flushed with hydrogen for 30 min then stirred for 24 h under a H_2 atmosphere. The reaction mixture is filtered and evaporated down under reduced pressure. The crude oil is further evaporated with H_2O (2 x 5 ml) and finally lyophilized giving the desired glycine mimic **102(3)**: ^{1}H NMR (D_2O, 400 MHz) δ 4.33 (m, 1 H), 3.68-4.0 (m, 6 H), 3.64 (t, J = 3.1 Hz, 1 H), 3.50-3.60 (m, 1 H), 2.81 (dd, J = 10.0, 14.7 Hz, 1 H), 2.57 (dd, J = 4.4, 14.7 Hz, 1 H), ^{13}C NMR (D_2O/DMSO, 100 MHz) δ 175.48, 77.42, 77.02, 73.14, 72.91, 69.56, 63.40, 37.57; HRMS calcd for $C_{10}H_{18}O_8N$ (M + H), 280.1032, found 280.1034.

Example B31: Preparation of 103(3)



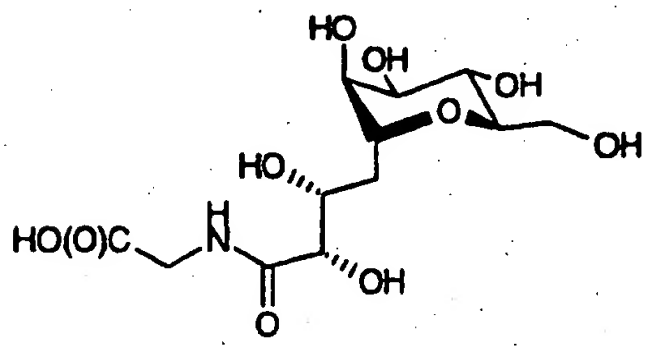
Starting from **103I(3) 103(3)** is prepared according to Example B30: ^{1}H NMR (D_2O, 400 MHz) δ 7.11 (d, J = 8.44 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 2 H), 4.53 (dd, J = 5.2, 8.40 Hz, 1 H), 4.21 (dd, J = 6.8, 6.8 Hz, 1 H), 3.58-3.79 (m, 5 H), 3.44-3.47 (m, 1 H), 3.12 (dd, J = 4.8, 13.9 Hz, 1 H), 2.87 (dd, J = 8.4, 14.0 Hz, 1 H), 2.70 (dd, J = 9.2, 15.2 Hz, 1 H), 2.44 (dd, J = 5.7, 15.2 H, 1 H); ^{13}C NMR (D_2O/DMSO, 100 MHz) δ 156.69, 132.96, 131.29, 117.81, 77.40, 76.80, 73.07, 72.87, 69.37, 63.21, 38.66, 37.44; MS calcd for $C_{17}H_{22}O_9N$ (M - H) 384, found 384.

Example B32: Preparation of 104(3)



Starting from **104I(3) 104(3)** is prepared according to Example B30: ^{1}H NMR (D_2O, 400 MHZ) δ 4.37-4.42 (m, 1 H), 4.32 (ddd, J = 1.8, 5.0, 5.0 Hz, 1 H), 3.87 (t, J = 2.9 Hz, 1 H), 3.79 (dd, J = 3.3, 9.0 Hz, 1 H), 3.71-3.77 (m, 2 H), 3.67 (dd, J = 9.2, 9.2 Hz, 1 H), 3.53-3.60 (m, 1 H), 2.80 (dd, J = 10.8, 14.8 Hz, 1 H), 2.55 (dd, J = 5.1, 14.9 Hz, 1 H), 2.46 (dd, J = 7.0, 7.0 Hz, 2H), 2.11-2.20 (m, 1 H), 1.90-2.02 (m, 1 H); ^{13}C NMR (D_2O/DMSO, 100 MHz) δ 192, 187, 181.8, 84.2, 83.7, 79.9, 76.2, 70.0, 44.3, 35.1; HRMS calcd for $C_{13}H_{22}O_{10}N$ (M + H), 352.1244, found 352.1238.

Example B33: Preparation of (2*S*,3*R*)-N-carboxylmethyl-2,3-dihydroxy-4-(α-D-manno-pyranosyl)-butyramide 105(3)

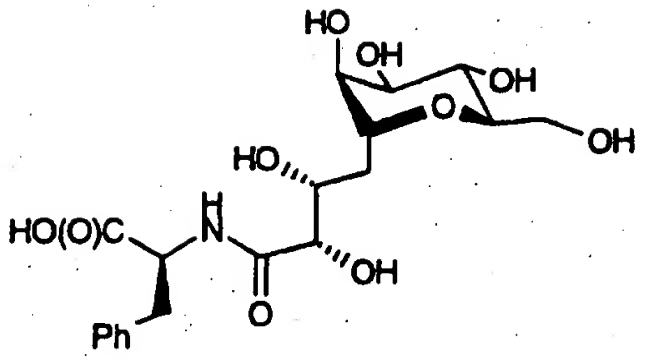


An ice-cold solution of LiOH (20 ml, 0.25 M in MeOH/H_2O 3:1) is added to ethyl ester **113(3)** (1 mmol) at 0°C and vigorous stirring is continued for 2 days at 4°C. The reaction mixture is acidified with cold 1 N HCl to pH 1-2 and quickly extracted with EtOAc, washed with brine and dried over $MgSO_4$. The solvent is removed in vacuo to give the pure acid **(A)** as a slightly yellow oil.

According to the general procedure B for peptide coupling, the above carboxylic acid (50 mg, 78 µmol) and H-Gly-OBn • p-TsOH (30 mg, 89 µmol) are treated with EDC (18 mg, 94 µmol), HOBt (12 mg, 92 µmol) and NMM (9.5 µl, 86 µmol) in DCM (0.9 ml) for 6 h to obtain the desired amide.

According to the general procedure A for hydrogenation of benzyl ethers, the above penta-benzyl compound (52.5 mg, 66.5 µmol) is deprotected and subsequently filtered through the Anotop 10 (0.02 µm) filter to yield polyhydroxyl compound **105(3)** after lyophilization. ^1H NMR (400 MHz, D_2O) δ 1.70 (1H, ddd, J = 14.2, 10.4, 3.1, H-1'a), 2.08 (1H, m, H-1'b), 3.53 (1H, ddd, J = 9.4, 6.0, 1.6, H-5), 3.64 (1H, t, J = 9.4, H-4), 3.71 (1H, dd, J = 12.1, 6.3, H-6a), 3.80 (1H, dd, J, = 9.3, 3.2, H-3), 3.86 (1H, dd, J = 12.2, 1.9, H-6b), 3.90 (1H, dd, J = 2.9, 1.7, H-2), 3.94 (1H, d, J = 17.9 gly-Ha), 4.04 (1H, d, J = 17.8, gly-Hb), 4.06-4.15 (2H, m, H-1, 2'), 4.16 (1H, d, J = 2.6, H-3'); ^{13}C NMR (100 MHz, D_2O) δ 33.05, 44.7 (br), 63.75, 69.84, 70.68, 73.17, 74.34, 76.17, 76.78, 77.29, 175.7 (br), 177.61; ESI MS calcd for $C_{12}H_{21}NO_{10}$ (M) 339, found (pos.: $M+H^+$) 340, (neg.: $[M-H]^-$) 338.

Example B33': Preparation of(2*S*,3*R*)-N-(benzyl-L-phenylalaninyl)-2,3-dihydroxy-4-(α-D-mannopyranosyl)-butyramide 106(3)



According to general procedure B for peptide coupling, previously prepared carboxylic acid **A** (51 mg, 79 µmol) and H-Phe-OBn • HCl (26 mg, 89 µmol) are treated with EDC (20 mg, 104 µmol), HOBt (14 mg, 104 mmol) and NMM (25 µl, 227 µmol) in DCM (0.9 ml) for 6 h to obtain the desired amide as a yellow oil.

According to the general procedure A for hydrogenation of benzyl groups , the above pentabenzyl compound (64 mg, 72.7 µmol) is deprotected and subsequently purified by Sephadex G 10 column filtration (H_2O) to yield polyhydroxylated compound **106(3)**. ^{1}H NMR (500 MHz, D_2O) δ 1.47 (1H, br t, J = 11.5, H-1'a), 1.89 (1H, br t, J = 12.9, H-1'b), 3.02 (1H, br s, β-Ha-phe), 3.13 (1H, br d, J = 10.8, β-Hb-phe), 3.40 (1H, dd, J = 7.3, 7.0), 3.54 (1H, t, J = 9.3), 3.62, (1H, dd, J = 11.7, 5.9), 3.68 (1H, br d, J = 7.0), 3.76 (1H, d, J = 11.3), 3.77 (1H, m), 3.93 (1H, br d, J = 7.7), 4.01 (1H, d, J = 11.1), 4.00-4.03 (1H, m), 4.54 (1H, br s), 7.19-7.29 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.17, 37.63, 62.09, 68.20, 68.86, 71.50, 72.64, 74.87, 75.58, 127.85, 129.46, 130.14, 137.57, 174.94 (br); HRMS calcd for $NaC_{19}H_{27}NO_{10}$ (M+Na) 452.1533, found 452.1545

Example C1:

(a) Preparation of liposome 59: 2.56 mg (0.0025 mmole) of lipid compound 58 and 17.79 mg (0.0475 mmole) of 57 are dissolved in $CHCl_3$/MeOH (10:1) solution. The solvents are evaporated and the residue is shielded from light and dried in vacuo. 5ml of HEPES buffer (20 mM, pH = 7.4) is added to yield a heterogeneous solution. To obtain a clear homogeneous solution, the lipid/buffer mixture is then sonicated with a probe-tip sonicator for at least 1h at the maximum power setting at which no frothing occurs and at which there is minimal disturbance of the solution surface. The temperature is maintained above the gel-liquid crystal phase transition point (T_m = 64°C) with the heat generated from sonication.

(b) Polymerization of liposome precursor to form lipid polymer 60: To polymerize the liposome, the liposome solution is transferred to a petri dish resting on a bed of wet ice, cooled to 0°C, and irradiated at 254 nm for 1h with a hand-held UV lamp placed in 1 cm about the

petri dish, yielding dark-blue paramagnetic polymerized liposomes (PPL). The PPL are then filtered through a 0.2µm mesh and collected (Procedure similar to that found in J. Am. Chem. Soc. 117:7301-7306 (1995); (T_m = 37°C, yellow PPL).

Example C2:

(a) Preparation of liposome precursor to compound 62: The liposome precursor to compound 62 is prepared according to Example C1(a) starting from 2.56 mg (0.0025 mmole) of lipid compound 58 and 17.79 mg (0.0475 mmole) of 61 (Avanti Plar Lipids Inc.).
(b) Polymerization of liposome precursor to form lipid polymer 62: Lipid polymer 62 is prepared according to Example C1(b) starting from the above precursor.

Example D: Protocol for Assaying Biological Activity

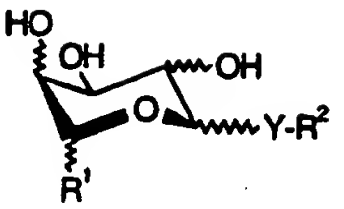
A soluble form of E-selectin (sol-E-selectin) is prepared for inhibition assays of the SLe^x mimetics. A 1.67 kbp DNA fragment encoding a truncated structural gene for E-selectin is isolated by PCR amplification of cDNA derived from mRNA that is isolated from IL-1 activated human endothelial cells. The cDNA is subcloned into the vector pBluescript II and is transfected into 293 cells. The clones are screened for the production of sol-E-selectin, and the clone 293#3 is selected as the stable cell line that produces the greatest amount of sol-E-selectin per cell. Sol-E-selectin is produced on a large scale from this line using a Nunc cell factory. Recombinant sol-E-selectin is isolated from the media using immunoaffinity chromatography.

The SLe^x mimetics are assayed for ability to block the adhesion of HL-60 cells to immobilized sol-E-selectin. Immobilized E-selectin is incubated first with inhibitor and then with HL-60 cells. The bound cells are lysed, and myeloperoxidase released from the bound cells is detected with o-phenylenediamine and hydrogen peroxide. The percentage inhibition is determined by comparing the absorbance of the resulting solution at 492 nm to that in wells containing no inhibitor.

Each data point in the E-selectin assay is a direct measure of cells bound using a quantitative enzyme assay. The values are then plotted to give the titration curve and IC_{50} values. The procedure described herein is adopted from Wong et. al. [J. Am. Chem. Soc. 177:66-79 (1995)]. In this assay the compounds of formula I show an inhibition at 3 mM of 70% to 80%, or an IC_{50} value of from 0.1 mM to 0.2 mM.

WHAT IS CLAIMED IS:

1. A compound of the formula I



(I)

wherein

(a) R^1 is CH_3;

Y is C_1-C_4alkylene which is unsubstituted or substituted by one or two substituents selected from OR^3 and $C(O)NH[CH_2]_mC(O)NHC_{10}$-$C_{16}$alkyl;

R^2 is $-NR^6R^7$;

R^3 is aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl or $CH_2C(O)NHC_1$-C_{20}alkyl which is unsubstituted or substituted by one or two $OC(O)C_{10}$-C_{16}alkyl;

R^6 is $C(O)CHR^8NHC(O)(CH_2)_qC(O)OH$;

R^7 is H or $(CH_2)_mC(O)NHC_{10}$-C_{16}alkyl;

R^8 is C_1-C_6alkyl unsubstituted or substituted with one or two OH;

m is a number from 1 to 6; and

q is 2 or 3; or

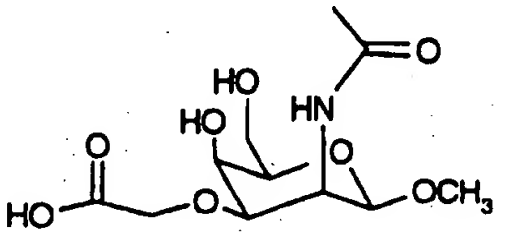
(b) R^1 is OH;

Y is $-CH_2-$;

R^2 is $-NR^6H$; and

R^6 is $C(O)$-C_1-C_{30}alkyl which is substituted by C(O)OH; or

(c) R^1 is a group of formula Ia



(Ia)

Y is $-CH_2-$; and

R^2 is OH; or

(d) R^1 is Y'-$R^{2'}$;

Y is $-CH_2-$;

R^2 is OH, $-O$-C_4-C_{30}alkyl or NHR^6;

Y' is $-CH_2-$ or $-O-CH_2-$;

R^2 is $-CHOHCHOHC(O)(CH_2)_nR^5$; $-CHOHCHOHC(O)[CH_2]_nC(O)OH$; $-CHOHCHOHC(O)CH_2CH[benzyl]C(O)OH$; $-CHOHCHOHC(O)NH(CHR^4)_nC(O)OH$; $-C(O)NHCH_2C(O)OH$; $C(O)NHCHR^4C(O)OH$; $-C(O)NHC_2$-C_4alkyl which is substituted by two C(O)OH or -C(O)NHphenyl which is substituted by one C(O)OH;

R^4 is H, C_1-C_6alkyl which is substituted by C(O)OH; CH_2hydroxyphenyl or benzyl;

R^5 is OPO_3H_2 or PO_3H_2;

R^6 is C_4-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl, aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl, O-C_4-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl, O-C_4-C_{30}alkenyl with 1 to 3 double bonds, O-C_6-C_{10}aryl, C(O)-C_1-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl or C(O)OH, C(O)-C_4-C_{30}alkenyl with 1 to 3 double bonds, $C(O)(CHR^8)_pNHC(O)(CH_2)_qC(O)OH$, $C(O)(CH_2)_mNHC_1$-C_6alkyl, or $C(O)(CH_2)_rCON(CH_2CONH(CH_2)CH_3)HCONH(CH_2)_sCH_3$;

R^8 is H or C_1-C_6alkyl unsubstituted or substituted with one or two OH;

m is a number from 1 to 6;

n is 1 or 2; and

the sum of p and q as well as of r and s has a value of from 2 to 22;

including their physiologically tolerated salts.

2. The compound according to claim 1 wherein

R^1 is CH_3; Y is C_1-C_4alkylene which is substituted by one or two OR^3; R^2 is $-NHR^6$; R^3 is aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl or $CH_2C(O)NHC_1$-C_{20}alkyl which is unsubstituted or substituted by one or two $OC(O)C_{10}$-C_{16}alkyl; R^6 is $C(O)(CHR^8)_pNHC(O)(CH_2)_qC(O)OH$; R^8 is C_1-C_6alkyl unsubstituted or substituted with one or two OH; p is 1; and q is 2 or 3; or

R^1 is CH_3; Y is C_1-C_4alkylene which is substituted by one or two OR^3; R^2 is $-NR^6R^7$; R^3 is aralkyl with C_1-C_6alkyl and C_6-C_{10}aryl or $CH_2C(O)NHC_1$-C_{20}alkyl which is unsubstituted or substituted by one or two $OC(O)C_{10}$-C_{16}alkyl; R^6 is $C(O)(CHR^8)_pNHC(O)(CH_2)_qC(O)OH$; R^7 is $(CH_2)_mC(O)NHC_{10}$-C_{16}alkyl; R^8 is C_1-C_6alkyl unsubstituted or substituted with one or two OH; p is 1; and q is 2 or 3; or

R^1 is OH; Y is $-CH_2-$; R^2 is $-NR^6H$; and R^6 is C(O)-C_1-C_{30}alkyl which is substituted by C(O)OH; or

R^1 is a group of formula Ia;

Y is $-CH_2-$; and R^2 is OH; or

R^1 is Y'-$R^{2'}$; Y is -CH_2-; Y' is -CH_2- or -O-CH_2-; R^2 is OH; $R^{2'}$ is CHOHCHOHC(O)$(CH_2)_nR^5$; R^5 is OPO_3H_2 or PO_3H_2; and n is 1 or 2; or

R^1 is Y'-$R^{2'}$; Y is -CH_2-; R^2 is OH; Y' is -CH_2-; $R^{2'}$ is -CHOHCHOHC(O)$(CH_2)_2$C(O)OH; -CHOHCHOHC(O)CH_2CH[benzyl]C(O)OH; -CHOHCHOHC(O)NHCHR^4C(O)OH; -C(O)NHCH_2C(O)OH or C(O)NHCHR^4C(O)OH; and R^4 is H, C_1-C_6alkyl which is substituted by C(O)OH; CH_2hydroxyphenyl or benzyl; or

R^1 is Y'-$R^{2'}$; Y is -CH_2-; Y' is -CH_2-; R^2 is -O-C_4-C_{30}alkyl and $R^{2'}$ is -C(O)NHC_2-C_4alkyl which is unsubstituted or substituted by two C(O)OH; or -C(O)NHphenyl which is substituted by one C(O)OH; or

R^1 is Y'-$R^{2'}$; Y is -CH_2-; Y' is -CH_2- or -O-CH_2-; R^2 is -NHR^6; $R^{2'}$ is - CHOHCHOHC(O)CH_2R^5 or C(O)NHCHR^4C(O)OH; R^5 is OPO_3H_2 or PO_3H_2; R^6 is C_4-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl, aralkyl with C_1-C_8alkyl and C_6-C_{10}aryl, O-C_4-C_{30}alkyl; C(O)-C_1-C_{30}alkyl which is unsubstituted or substituted by C_6-C_{10}aryl or C(O)OH; C(O)$(CH_2)_p$NHC(O)$(CH_2)_q$C(O)OH; C(O)$(CH_2)_m$NHC_1-C_6alkyl; or C(O)$(CH_2)_r$CON(CH_2CONH$(CH_2)CH_3$)HCONH$(CH_2)_sCH_3$; m is a number from 1 to 6; n is 1 or 2; and the sum of p and q as well as of r and s has a value of from 2 to 22.

3. A process for the preparation of a compound according to claim 1 wherein the corresponding radicals -Y-R^2 and -Y'-$R^{2'}$ are coupled, optionally via more than one step, to the corresponding sugar moiety.

4. A compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.

5. A method for preventing or treating conditions or diseases which are mediated by the binding of selectin in cellular adhesion in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

7. A compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof for use in the manufacturing of a medicament for use in the method according to claim 5.